A Randomized Phase 2 Study of Long-Acting TransCon GH vs Daily GH in Childhood GH Deficiency

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Context: TransCon Growth Hormone (GH) (Ascendis Pharma) is a long-acting recombinant sustained-release human GH prodrug in development for children with GH deficiency (GHD).

Objective: To compare the pharmacokinetics, pharmacodynamics, safety, and efficacy of weekly TransCon GH to that of daily GH in prepubertal children with GHD.

Design: Randomized, open-label, active-controlled study of three doses of weekly TransCon GH versus daily Genotropin (Pfizer).

Setting: Thirty-eight centers in 14 European countries and Egypt.

Patients: Prepubertal male and female treatment-naïve children with GHD (n = 53).

Interventions: Subjects received one of three TransCon GH doses (0.14, 0.21, or 0.30 mg GH/kg/wk) or Genotropin 0.03 mg GH/kg/d for 26 weeks.

Main Outcome Measures: GH and insulinlike growth factor-1 (IGF-1) levels, growth, adverse events, and immunogenicity.

Results: Both GH maximum concentration and area under the curve were similar following TransCon GH or Genotropin administration at comparable doses. A dose response was observed, with IGF-1 standard deviation scores increasing into the normal range for all three TransCon GH doses. Annualized mean height velocity for the three TransCon GH doses ranged from 11.9 cm to 13.9 cm, which was not statistically different from 11.6 cm for Genotropin. Adverse events were mild to moderate, and most were unrelated to the study drug. Injection site tolerance was good. One TransCon GH subject developed a low-titer, nonneutralizing antibody response to GH.

Conclusions: The results suggest that long-acting TransCon GH is comparable to daily Genotropin for GH (pharmacokinetics) and IGF-1 (pharmacodynamics) levels, safety, and efficacy and support advancement into phase 3 development. (***J Clin Endocrinol Metab*** **102: 1673–1682, 2017)**

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Abbreviations: AE, adverse event; AUC, area under the curve; BMI, body mass index; C_{max}, maximum concentration; ECG, electrocardiogram; GH, growth hormone; GHD, growth hormone deficiency; HbA1c, hemoglobin A1c; HV, height velocity; IGF-1, insulinlike growth factor-1; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation; SDS, standard deviation score.

Human growth hormone (GH), produced by and secreted from the pituitary gland, is essential for optimal body growth and key functions such as glucose control, lipid metabolism, and bone turnover. GH binds to specific cell surface receptors and exerts its effects both directly in peripheral tissues (such as epiphyseal chondrocytes) and indirectly via insulinlike growth factor-1 (IGF-1). GH and IGF-1 work in concert, with important effects on growth control and body composition. Although acting synergistically on bone, GH and IGF-1 have opposing effects on adipose tissue; GH is lipolytic, whereas IGF-1 is lipogenic (1).

Recombinant human GH, also known as somatropin, became commercially available in the mid-1980s. The amino acid sequence of somatropin is identical to the 22 kDa growth hormone secreted by the pituitary. To date, childhood GH deficiency (GHD) treatment consists of daily subcutaneous GH injections, and many GH products are available.

In the past, children with GHD who began daily GH replacement were expected to achieve normal adult height. However, outcomes have not matched expectations; most children with GHD who are treated with GH do not obtain such stature (2). A major reason is poor adherence. The explanations for this are varied (not to mention inconsistent across observational studies) but include perceived ineffectiveness, side effects, and social issues among pediatric patients (and their parents), and denial and peer pressure among adolescent patients (3, 4). Nonadherence also increases with time, thus impairing therapeutic response (5, 6). Thus, optimizing patient adherence is critical, as are age of diagnosis and GH initiation.

The burdensome nature of a daily injectable GH makes a once-per-week, long-acting formulation attractive. Ideally, such a long-acting product would have similar safety, efficacy, and immunogenicity profiles compared with existing daily options, which could improve adherence and compliance and, by extension, final height. Furthermore, given both direct and IGF-1–mediated GH effects, optimizing IGF-1 levels in relationship to GH in target tissues is a desirable goal.

Over the years, there have been multiple attempts to develop long-acting GH formulations. TransCon Growth Hormone (Ascendis Pharma, Hellerup, Denmark) is a sustained-release, inactive prodrug that consists of a parent drug, GH, that is transiently bound to the methoxypolyethylene glycol molecule via a proprietary linker. The inert methoxypolyethylene glycol molecule acts as a carrier, extending GH circulation time in the body through a shielding effect that minimizes renal excretion and receptor binding (Fig. 1).

Over a one-week period, TransCon GH releases fully active, unmodified GH via autohydrolysis of the TransCon Linker in a controlled manner on the basis of naturally occurring hydrolysis that occurs at physiologic pH and temperature. As such, the TransCon technology is designed to maintain the same mode of action and distribution as GH administered daily by allowing sustained release of recombinant GH.

The purpose of this investigation was to compare the pharmacokinetics (PKs), pharmacodynamics (PDs), safety, and efficacy of three TransCon GH doses to that of commercially available daily recombinant GH in prepubertal children with GHD.

Methods

Study design

This was a phase 2, randomized, open-label, active-controlled study of three different doses of weekly TransCon GH compared with daily Genotropin (Pfizer, New York, NY). The study was conducted at 38 centers in 14 countries in Europe and Egypt. Prior to any study-specific procedure, institutional review board and independent ethics committee approval and signed informed consents from subject parent(s)/legal guardian(s) were obtained. The ClinicalTrials.gov identifier is NCT01947907.

Population

Male and female prepubertal subjects [Tanner stage 1 boys (age 3 to 12) or girls (age 3 to 11)] diagnosed with GHD on the

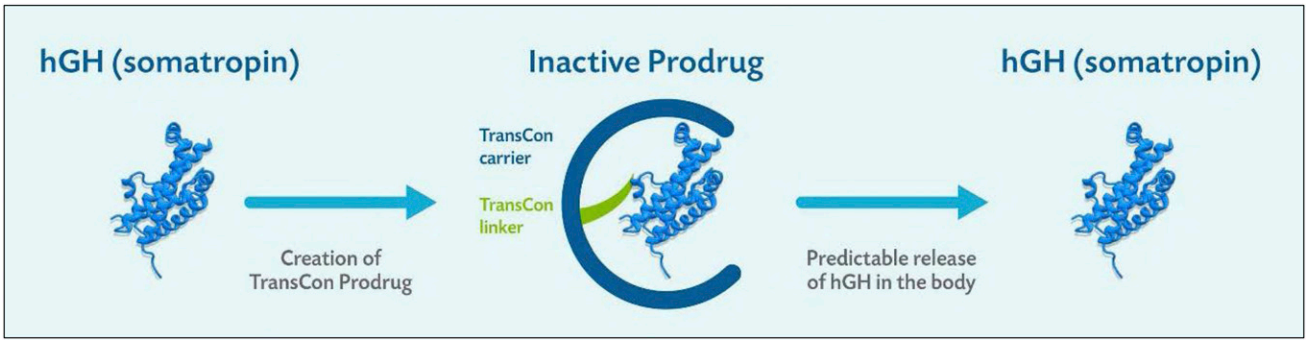

Figure 1. TransCon GH, a sustained-release inactive prodrug consisting of a parent drug, unmodified GH, that is transiently bound to a carrier, methoxypolyethylene glycol, via a proprietary linker that is autohydrolyzed under physiologic pH and temperature. hGH, human growth hormone.

basis of auxological and biological criteria were enrolled. Auxological criteria for GHD diagnosis included short stature [height defined as 2.0 standard deviations (SDs) below the mean for age and sex] (7), inadequate height velocity (HV) (defined as 1.0 SD below the mean for age and sex) (8), body mass index (BMI) within 2.0 SDs of the mean for age and sex, and bone age no greater than chronological age (on the basis of x-rays of the left hand and wrist and determined using a central bone age reader). Biological criteria for GHD diagnosis included two different GH stimulation tests with peak GH levels ≤10 ng/mL (the second test was performed during screening and centrally assayed) and baseline IGF-1 at least 1.0 SD below the mean for standardized age and sex. Subjects were excluded if they had received prior GH or IGF-1 treatment, had psychosocial dwarfism, idiopathic (or other causes of) short stature, a cranial tumor on magnetic resonance imaging of the head, GHD secondary to malignancy, abnormal fundoscopy, abnormal *SHOX1* gene analysis, Turner syndrome by karyotype, presence of anti-GH binding antibodies, and/or closed epiphyses.

Study protocol

Subjects attended six visits, one screening visit (to determine eligibility) and five subsequent visits during 26 weeks of treatment (weeks 1, 5, 13, and 26, along with day 1 of week 27 for follow-up). The screening visit included a complete medical history and physical examination (vital signs; weight; height measurement using a wall-mounted, calibrated stadiometer; and fundoscopy), electrocardiogram (ECG), and pubertal status assessment on the basis of Tanner stages. Select laboratory tests were also performed, including lipids, glucose, hemoglobin A1c (HbA1c), insulin, hormones, urinalysis, hematology, and chemistry. Subsequent visits included a physical examination, ECG, and repeat laboratory tests.

Eligible subjects were randomly assigned to receive one of three subcutaneous doses of TransCon GH (ACP-001), *i.e.*, 0.14, 0.21, or 0.30 mg GH/kg/wk (cohorts 1 to 3), or Genotropin administered daily at a dose of 0.03 mg GH/kg/d (cohort 4; equivalent to TransCon GH 0.21 mg GH/kg/wk) for 26 weeks. The study drug was administered on the basis of the subject's weight measured prior to dosing during week 1 and, if necessary, adjusted on the basis of weight prior to dosing during week 13.

PKs, PDs, safety, and efficacy assessments

Blood samples for PK and PD profiling were drawn at baseline and up to 168 hours after the dose during weeks 1 and 13. Additional samples were drawn at baseline (day 1) during weeks 5 and 26 and at follow-up on day 1 of week 27. GH was centrally quantified in serum by a validated sandwich enzyme-linked immunosorbent assay (Celerion, Lincoln, NE), whereas IGF-1, the primary PD biomarker, was centrally quantified in serum by a validated chemiluminescence immunoassay (Laboratorium für Klinische Forschung, Schwentinental, Germany) using a multidiscipline automated system (IDS iSYS; Immunodiagnostic Systems, Bolden, UK). IGF-1 measurements were based on normative values, and IGF-1 standard deviation score (SDS) calculations were based on sex- and age-specific reference ranges published by Bidlingmaier *et al.* (9).

For PK assessments during weeks 1 and 13, maximum GH concentration (C_{max}) was defined as the highest postdose concentration. Area under the curve (AUC) for TransCon GH–treated subjects was calculated on the basis of the drug concentration at time 0 to 168 hours following the dose using the linear trapezoidal rule; both uncorrected and baseline (predose week 1) corrected AUCs were computed. AUC for Genotropin-treated subjects was calculated on the basis of the drug concentration at time 0 to 24 hours following the dose multiplied by seven to be comparable to TransCon GH. For PD assessment, time to maximum efficacy (T_{Emax}) was defined as the time needed to attain the highest IGF-1 response (E_{max}). IGF-1 area under the efficacy curve for both TransCon GH–treated and Genotropin-treated subjects was calculated as for PKs.

To ensure that GH and IGF-1 levels at baseline did not affect PK and PD calculations, posttreatment concentration data were adjusted in the following two ways:

(1) Absolute baseline correction:

$$C_{corrected,t} = C_{measured,t} - C_{measured,pre\text{-}dose}$$

(2) Percent baseline correction:

$$C_{corrected,t} = \left(C_{measured,t} - C_{measured,pre\text{-}dose}\right) \times 100 / C_{measured,pre\text{-}dose}$$

Subjects were monitored for adverse events (AEs), defined as any undesirable sign, symptom, or medical condition occurring after drug therapy initiation, and serious AEs, defined as any untoward medical occurrence that was life-threatening, required inpatient hospitalization, and/or resulted in significant disability or death.

Subjects were also monitored for local injection site tolerability. Pain was assessed on the basis of the Wong-Baker FACES Pain Rating Scale (scale includes scores ranging from 0 to 5) (10); results were included if the pain was over score 3 and/or of a duration >15 minutes. Injection site reactions were assessed on a scale of 0 to 3 on the basis of the presence of redness, bruising, swelling, and/or itching.

Using validated assays, immunogenicity against GH-binding antibodies was assessed at baseline for all visits by a tiered approach (binding, confirmation, titer) and performed centrally (Eurofins Pharma Bioanalysis Services UK, Abingdon, UK). Serum samples confirmed positive for anti–GH-binding antibodies were assessed for anti–GH-neutralizing antibody activity.

Statistical analysis

Demographic characteristics and peak GH at screening as well as GH, IGF-1, height, HV, and anti-GH antibodies by visit were analyzed by descriptive statistics. Height was measured after 6 months of therapy and annualized HV (cm/y) was extrapolated. The BMI SDS was calculated using Growth Analyzer Research Calculation Tools, version 4.0.30 (Rotterdam, the Netherlands). Analysis of covariance for weeks 13 and 26 end points, including baseline and change in GH, IGF-1, height, and HV for each cohort, was used to estimate least-square means and 95% confidence intervals. AE summary incidence rates, intensity, and relationship to the study drug were calculated. If a subject experienced more than one AE for the same period, only the AE with the strongest relationship or greatest intensity was included.

Results

Subjects

A total of 170 subjects were screened. Fifty-five subjects met inclusion criteria and were randomly assigned.

Two subjects withdrew after random assignment but before the first dosing and were thus excluded from further analyses. The remaining 53 subjects were randomly assigned to four groups. Cohort 1 (n = 12) received TransCon GH 0.14 mg/kg/wk. Cohort 2 (n = 14) received TransCon GH 0.21 mg/kg/wk. Cohort 3 (n = 14) received TransCon GH 0.30 mg/kg/wk. Cohort 4 (n = 13) received Genotropin 0.03 mg/kg/d (equivalent to TransCon GH 0.21 mg/kg/wk).

The cohorts were balanced with respect to sex, race, age, and baseline IGF-1 levels. All subjects were white; 38 (72%) were male and 15 (28%) were female (Table 1). The mean GH on the stimulation tests for the four cohorts was 5.0 ng/mL. At visit 1, the mean age was 8.0 years and the mean height SDS was −3.1.

PKs

The mean GH serum concentration profiles following subcutaneous administration of TransCon GH in week 13 are presented in Fig. 2. TransCon GH released GH in a sustained manner over 168 hours, returning back to baseline at the end of the interval for all three doses without considerable accumulation. Median time to GH C_{max} with TransCon GH was 12 to 48 hours, delayed compared with Genotropin administration (Fig. 3). GH exposure (C_{max} and AUC) after administration of TransCon GH or Genotropin at comparable weekly doses was similar.

PDs

The mean IGF-1 SDS at study baseline was approximately two SDSs below predicted for age and sex in cohorts 1 to 3 (Table 1). Following TransCon GH treatment, mean IGF-1 levels and IGF-1 SDSs increased above study baseline, with IGF-1 levels higher at week 13 than week 1. This is consistent with multiple GH doses being required to establish a stable weekly IGF-1 response. Predose (trough) IGF-1 responses were consistent from week 5 onward (data not shown). Following T_{Emax}, the IGF-1 response decreased, although levels did not reach study baseline concentrations prior to the next dose but rather remained at predose levels attained from week 13 onward (Fig. 4). At week 13, a dose response was evident in mean absolute baseline–corrected data; IGF-1 SDSs increased into the normal range (−1.0 to 2.0 SDSs) on all three doses of TransCon GH.

Individual IGF-1 SDSs were <2.0 for all cohort 1 subjects throughout the study. Two subjects in cohort 2 had IGF-1 SDS excursions >2.0 during week 13. Four subjects (one in week 1 and three in week 13) in cohort 3 had IGF-1 SDSs >2.0. One additional subject in cohort 3 had an IGF-1 SDS excursion >3.0 during week 13. All excursions above SDS 2.0 and 3.0 were transient, and none resulted in dose modification. All subjects receiving Genotropin had IGF-1 SDSs <1.0 for both week 1 and week 13.

Efficacy

Height was measured at 26 weeks. Among the three weekly TransCon GH doses, mean annualized HV extrapolated from the 26-week measurements ranged from 11.9 cm/y to 13.9 cm/y (Fig. 5). Mean annualized HV was 11.6 cm/y for daily Genotropin compared with 12.9 cm/y at the equivalent weekly TransCon GH dose of 0.21 mg/kg/wk. At the end of 26 weeks, the minimum annualized HV of 6.42 cm/y occurred at the lowest TransCon GH dose (cohort 1) compared with 6.22 cm/y in the Genotropin group, whereas the maximum annualized HV

Table 1. Demographic and Baseline Characteristics at Visit 1[a]

	Cohort 1: TransCon GH 0.14 mg/kg/wk (n = 12)	Cohort 2: TransCon GH 0.21 mg/kg/wk (n = 14)	Cohort 3: TransCon GH 0.30 mg/kg/wk (n = 14)	Cohort 4: Genotropin 0.21 mg/kg/wk (n = 13)
Male (female)	9 (3)	10 (4)	9 (5)	10 (3)
Mean age, y	8.2 (2.9)	8.4 (2.1)	7.5 (2.8)	7.7 (2.5)
Mean bone age, y	5.2 (2.3)	6.5 (2.1)	4.7 (2.6)	4.9 (2.3)
Mean weight, kg	19.6 (5.6)	19.5 (4.9)	18.9 (6.6)	19.6 (6.3)
Mean height, cm	110.6 (16.3)	113.3 (11.6)	106.8 (16.0)	107.4 (15.0)
Mean height SDS	−3.1 (1.1)	−2.8 (0.4)	−3.2 (1.0)	−3.3 (1.1)
Mean BMI, kg/m^2	15.8 (1.7)	15.0 (1.3)	16.1 (1.8)	16.6 (1.9)
Mean BMI SDS	−0.4 (1.1)	−0.9 (0.7)	−0.1 (1.0)	0.2 (0.8)
Mean GH stimulation test, ng/mL[b]	5.1 (3.2)	5.2 (2.6)	4.4 (2.8)	5.2 (3.1)
Mean IGF-1, ng/mL[c]	80.8 (52.2)	80.3 (48.4)	62.5 (39.8)	53.8 (35.2)
Mean IGF-1 SDSc	−2.0 (0.7)	−2.0 (0.8)	−2.2 (0.7)	−2.5 (0.9)

Values are presented as means, with SDs in parentheses, unless otherwise noted.

[a]Unless otherwise noted.

[b]At screening.

[c]Uncorrected.

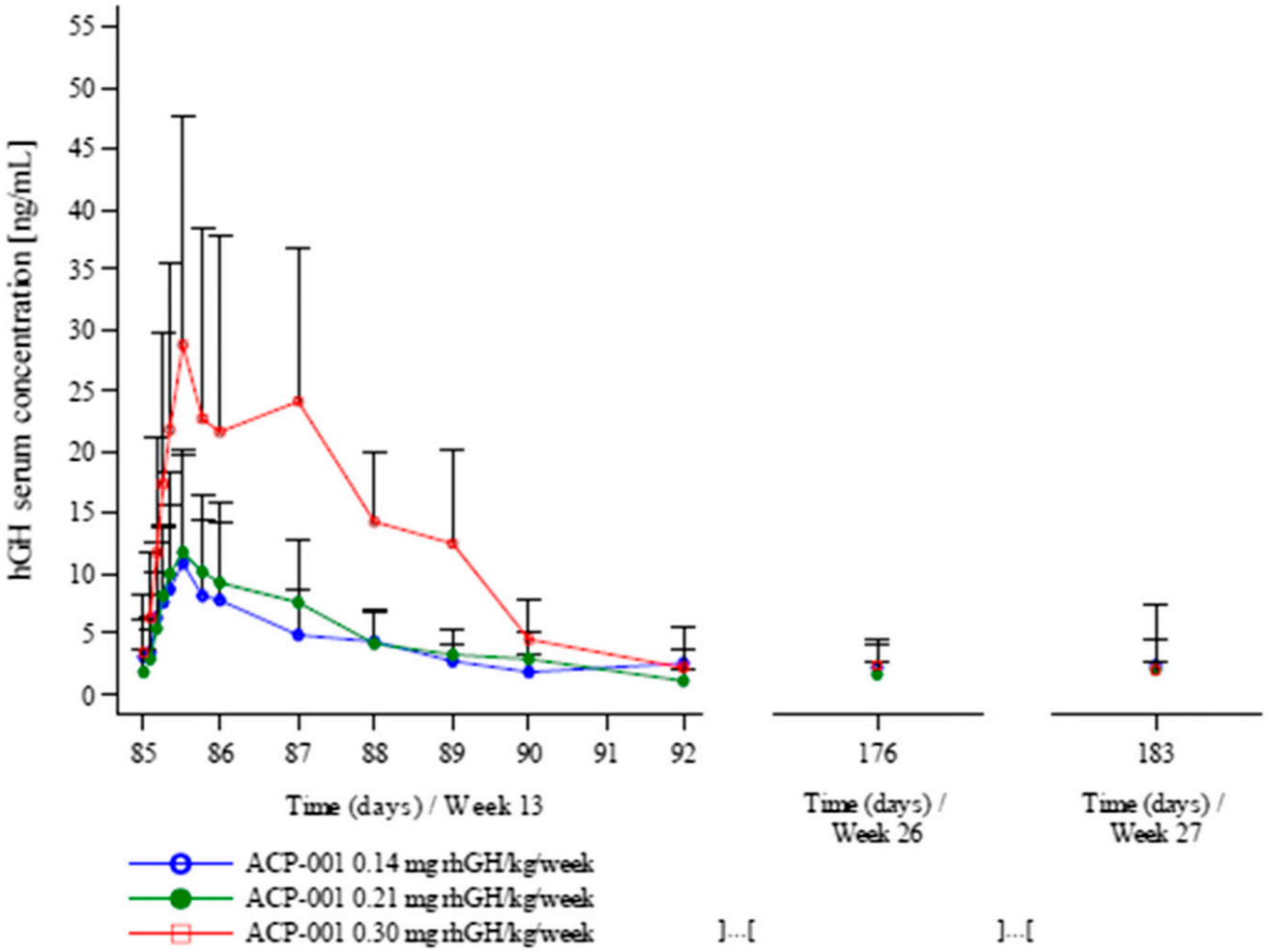

Figure 2. GH serum concentration (ng/mL), arithmetic means (+ SDs), linear scale, untransformed data, after weekly administration of TransCon GH (ACP-001) at week 13. hGH, human GH; rhGH, recombinant human GH.

of 22.00 cm/y occurred at the highest TransCon GH dose (cohort 3) compared with 19.25 cm/y in the Genotropin group. However, the differences across the four cohorts were not statistically significant. Δheight SDSs increased from 0.7 to 0.9 in the three TransCon GH cohorts compared with 0.6 in the Genotropin cohort (Supplemental Fig. 1).

Safety

There were no life-threatening AEs or AEs leading to death, nor did any AE lead to subject withdrawal. Twenty-nine subjects (54.7%) reported 53 AEs; all were mild to moderate in intensity, and most were considered to be either unrelated or unlikely to be related to the study drug. Supplemental Table 1 describes treatment-emergent AEs occurring in more than one subject in any cohort.

One subject (1.9%) reported a serious AE (inguinal hernia) assessed as mild in severity and considered unlikely to be related to the study drug. Two subjects (3.8%) reported AEs with possible or probable relationships to the study drug. The first subject, who received TransCon GH (cohort 1), reported mild decreased appetite, nausea, and vomiting, which were assessed as possibly related to the study drug. The second subject, who received TransCon GH (cohort 3), experienced mild iron deficiency anemia that was assessed as likely related to the study drug.

Overall, AE incidence was similar across all three TransCon GH doses (range 43% to 58%) and Genotropin (61.5%). For all cohorts, the AEs observed were consistent with the known safety profile of daily somatropin.

TransCon GH and Genotropin tolerability were similar. Injection site reactions were reported by 25 subjects (seven in cohort 1; six in cohorts 2, 3, and 4, respectively), collectively, 141 times. Pain was most common, reported by 22 subjects (five in cohorts 1 and 2, respectively; six in cohorts 3 and 4, respectively), collectively, 109 times. There was no injection site nodule formation or lipoatrophy. Injection site reactions were generally mild and transient and did not increase with

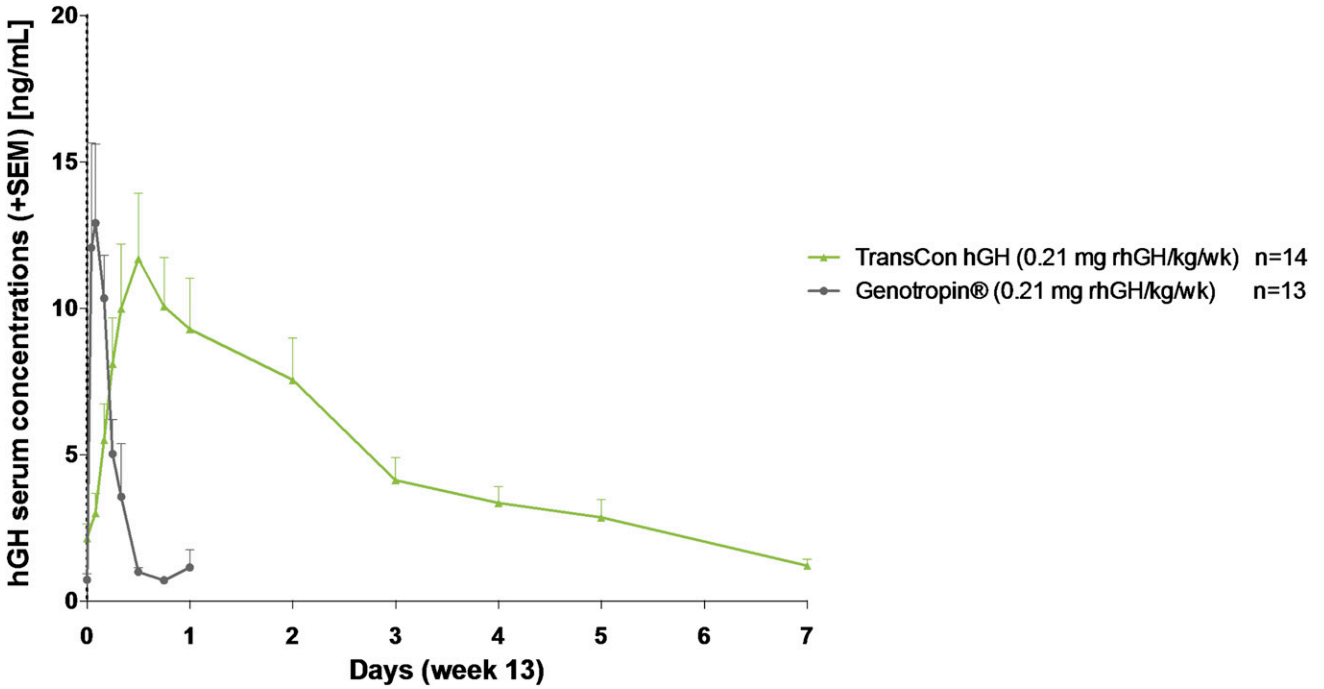

Figure 3. GH serum concentration (ng/mL), arithmetic means [+ standard error of the mean (SEM)], linear scale, untransformed data, after weekly administration of TransCon GH (0 to 168 hours) or daily administration of Genotropin (0 to 24 hours) at week 13. hGH, human GH; rhGH, recombinant human GH.

TransCon GH dose. There were no notable differences in injection site reactions between TransCon GH and Genotropin.

No neutralizing anti–GH-binding antibodies were detected. One subject (one of 40; 2.5%) receiving TransCon GH (cohort 1) developed a treatment-emergent, anti-GH immune response that was initially detected at week 13. Titration at week 26 indicated the presence of very low titers of nonneutralizing anti–GH-binding antibodies that did not appear to affect PK or PD profiles; the subject had an annualized HV of 19.0 cm, in the top fiftieth percentile of cohort 1.

Across all treatment groups, no safety concerns were detected by physical examination (including vital signs and fundoscopy), ECG, or clinical laboratory parameters (glucose, HbA1c, lipids, hormones, urinalysis, hematology, and chemistry); data not shown. A few fasting glucose and insulin levels were above the normal range. However, prior or subsequent levels were normal, suggesting that subjects were not fasting at the time of testing. No differences were observed for lipids, glucose, HbA1c, or insulin, suggesting that the effect of TransCon GH on lipid and glucose metabolism was comparable to Genotropin under study conditions (Supplemental Table 2).

Other results

Twenty-seven of 40 (68%) subjects had a BMI SDS below zero at visit 1. The mean average change in BMI from visit 1 to visit 5 for cohorts 1 to 3 and cohort 4 was 0.03 and −0.66, respectively. The overall mean change in BMI SDS for cohorts 1 to 3 and cohort 4 was −0.08 and −0.45, respectively.

Discussion

The results of this TransCon GH study demonstrated that serum GH, as measured by C_{max} and AUC over seven days, was within physiological range and comparable to a weekly cumulative dose of daily Genotropin, which is interesting with respect to both safety and efficacy considerations. IGF-1 changes demonstrated a dose-response relationship to TransCon GH, whereas IGF-1 SDSs of all three TransCon GH doses normalized. Mean annualized HV ranged from 11.9 cm/y to 13.9 cm/y and compared favorably with 11.6 cm/y for Genotropin administered daily. AEs were mild to moderate, and most were unrelated to or unlikely to be related to the study drug. TransCon GH injection site reactions were comparable to those of daily GH, and with no lipoatrophy or nodule formation observed. No neutralizing anti–GH-binding antibodies were detected. The mean BMI SDS was stable across the three TransCon GH cohorts, as expected, compared with daily GH.

Depending on the methodology used, the prevalence of daily GH nonadherence ranges from 5% to 82% (3). A study in New Zealand by Cutfield *et al.* (6) demonstrated that two-thirds of patients who missed one or more doses per week showed significantly reduced linear growth compared with compliant patients. Thus, short-acting

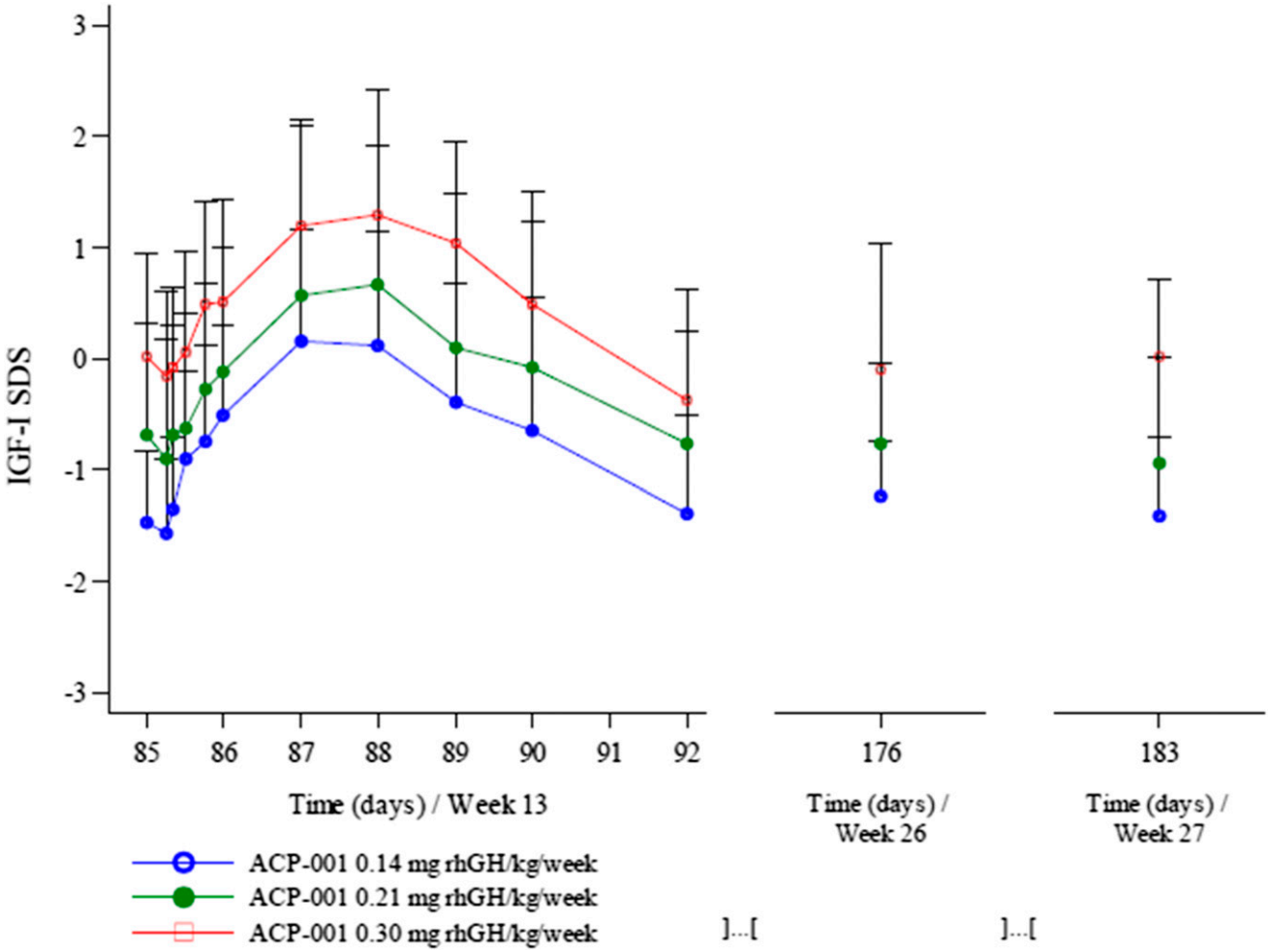

Figure 4. IGF-1 SDS, arithmetic means (+ SDs), linear scale, untransformed data, after weekly administration of TransCon GH (ACP-001) at week 13.

daily GH products may be both safe and effective, but this is of little consolation if they are not taken as prescribed. It is well established that the simpler a regimen, the more likely a patient will be to adhere to it, making long-acting GH ideal for hormone-deficient children and adolescents, a patient population that is subject to long-term daily GH injections. Thus, the Growth Hormone Research Society advised that developing a long-acting compound is a worthy objective (*5*).

A long-acting GH should be on par with daily GH in terms of safety, efficacy, tolerability, and immunogenicity. TransCon GH is designed to leverage the inherent low immunogenicity of unmodified GH. In the prodrug form, the carrier shields both the protein and the protein-carrier interface. Following release from the prodrug, unmodified GH has the same low immunogenic potential as daily GH. In this study, no neutralizing anti–GH-binding antibodies were detected in any subjects receiving TransCon GH. Only one subject developed a low-titer, treatment-emergent, nonneutralizing anti–GH-binding antibody response and yet had a subsequent annualized HV above the cohort median. Overall, the immunogenicity frequency and profile of TransCon GH was similar to that of daily GH.

Through a complex process of visceral fat accumulation and insulin resistance, GHD causes abnormal body composition, dyslipidemia, diabetes mellitus, low-grade chronic inflammation, and, collectively, an increased risk of cardiovascular disease and mortality (11). Given the lipolytic effect of GH, GH replacement results in a reduction in fat mass, particularly in the abdomen (12). In our study, the mean BMI SDS across TransCon GH cohorts was stable compared with a moderate decrease in the Genotropin cohort; this moderate BMI SDS decrease was observed in the setting of a slightly higher mean BMI at baseline. Given TransCon GH's mechanism of action of releasing free GH, and because GH and IGF-1 levels were comparable to Genotropin, careful BMI monitoring over a longer TransCon GH treatment period in a larger cohort of subjects with GHD is warranted.

Besides cardiac inflammation, children with GHD also have reduced cardiac mass, impaired diastolic filling, and reduced left ventricular response, which may be at least partially reversed with GH (13). However, whereas GH deficiency is problematic, so is GH excess. High endogenous

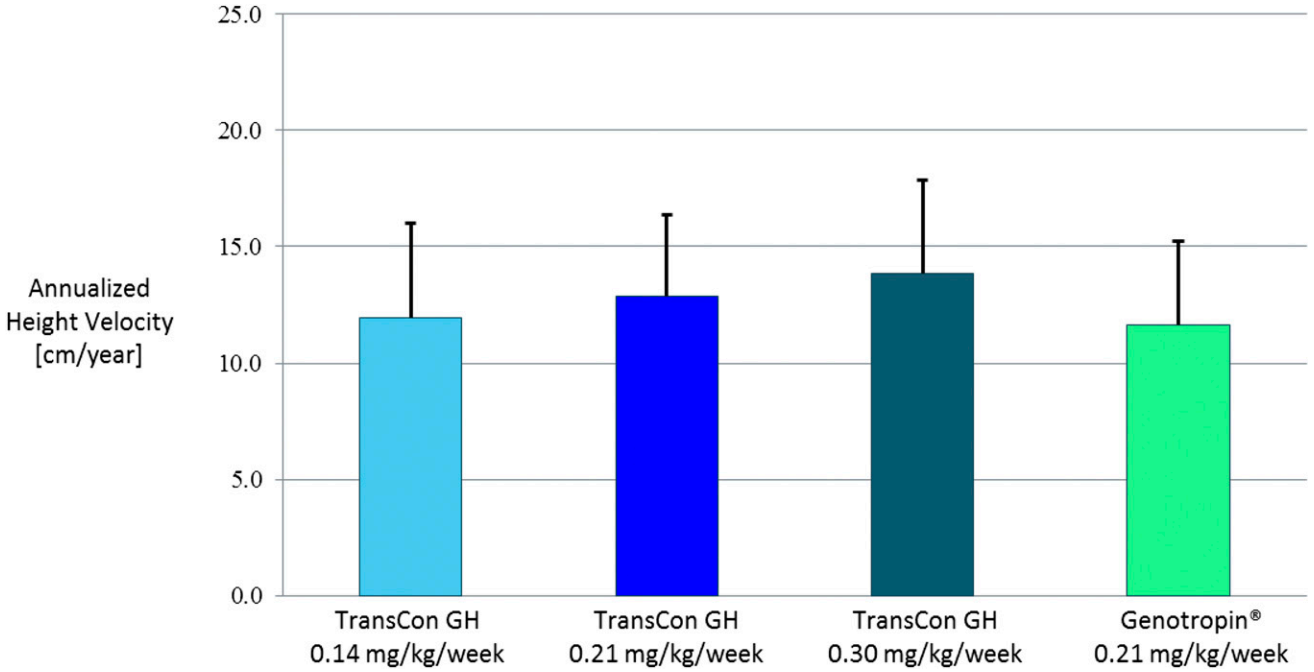

Figure 5. Annualized HV (means + SDs) in 53 subjects after 26 weeks of TransCon GH vs Genotropin treatment.

GH levels can be deleterious, as demonstrated by the pathologic states of both acromegalic cardiomyopathy and acromegalic regurgitant valvular heart disease (13, 14). In a study of young, healthy, adult volunteers who received high-dose GH (0.06 mg/kg/d, *i.e.*, twice the dose of Genotropin used in this study) for four weeks, participants developed a high cardiac output state with concentric left ventricular remodeling (15). These subjects had high IGF-1 levels, as do patients with acromegaly. Unlike some long-acting products associated with supraphysiological GH levels, TransCon GH administration leads to both GH and IGF-1 levels that are similar to those seen with daily GH at comparable weekly doses; many years of safety data have been gathered on daily GH (16).

TransCon GH was effective; subjects achieved height and annualized HV comparable to that of subjects receiving daily GH. At all three doses given for 26 weeks, TransCon GH also outperformed the mean HV of 9.2 cm in the first year that was observed among compliant (*i.e.*, those taking six or more injections per week) prepubertal children with idiopathic GHD in the Kabi Pharmacia International Growth Study Database (17, 18). This translates into a likelihood that children with GHD treated with TransCon GH may reach their adult height target as compared with those taking daily GH alternatives. Given that TransCon GH is administered weekly—a more acceptable frequency for children and adolescents with GHD—it stands to reason that when six injections in a week are eliminated, and dosing follows an easy-to-remember schedule, compliance may improve, and optimal adult height is more likely to be achieved.

TransCon GH was well tolerated, which is not surprising, given the similar GH and IGF-1 exposure achieved with TransCon GH compared with daily GH. Excursions above 2.0 IGF-1 SDSs across cohorts were infrequent, which is an important finding, given that high IGF-1 levels are associated with certain types of cancers (19). Weekly TransCon GH administration allows clinicians to titrate dosing on the basis of IGF-1 levels, with the goal of maintaining the range at <2.0 SDSs. It was only in cohort 3, at the highest TransCon GH dosing, that an IGF-1 SDS >3.0 was seen, and this occurred in only one subject and was transient. These results are consistent with daily GH excursions; in their study, Cohen *et al.* (20) found that 30% of patients who received daily GH conventionally dosed at 0.04 mg/kg/d (closest in dosing to TransCon GH cohort 3 recipients) had IGF-1 levels of >2.0 SDSs. Of note, rigorous IGF-1 measurements are critical to GH dose titration. Because IGF-1 levels and reference intervals vary from assay to assay, it is important to use consistent and well-controlled IGF-1 testing methodologies and the same assay at each patient follow-up visit (21).

This study had limitations. An approved long-acting GH product with the same safety, efficacy, tolerability, and immunogenicity as daily GH was not available as an active comparator, making blinding impossible. The sample size was small; only 40 subjects received TransCon GH. However, despite the widely divergent prevalence range cited in the literature of one in 3480 to one in 30,000 (22), childhood GHD is relatively uncommon; a large sample size is not realistic. Finally, this study lasted

only 26 weeks, a relatively short time in the overall growth period of a child.

Overall, long-acting TransCon GH, conveniently dosed with a milligram-to-milligram conversion to achieve doses similar to those of commercially available daily GH products, was comparable to Genotropin in terms of GH and IGF-1 exposure, safety, and efficacy. The results of this phase 2 study supported advancement of TransCon GH into phase 3 development.

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