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The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

Submitted: November 23, 2016
Accepted: February 07, 2017
First Online: February 14, 2017

Study of TransCon Growth Hormone in Childhood GHD

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Received 23 November 2016. Accepted 07 February 2017.

Context:
TransCon Growth Hormone (GH) is a long-acting recombinant sustained-release human GH prodrug in development for children with growth hormone 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 compared to daily Genotropin.
Setting:
Thirty-eight centers in 14 European countries and Egypt.
Patients:
Prepubertal male and female treatment-naïve children with GHD (n=53).
Intervention(s):
Subjects received one of three TransCon GH doses (0.14, 0.21, or 0.30 mg GH/kg/week) or Genotropin 0.03 mg GH/kg/day for 26 weeks.
Main Outcome Measures:
GH and insulin-like growth factor-1 (IGF-1) levels, growth, adverse events, 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 (SDS) 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, non-neutralizing antibody response to GH.
Conclusions:
The results suggest that long-acting TransCon GH was comparable to daily Genotropin for GH (pharmacokinetics) and IGF-1 (pharmacodynamics) levels, safety, and efficacy and supported advancement into Phase 3 development.

In 53 prepubertal children with GHD, annualized mean height velocity for three doses of weekly TransCon GH was not statistically different from daily Genotropin, and TransCon GH was well tolerated.

INTRODUCTION

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 insulin-like growth factor-1 (IGF-1). GH and IGF-1 work in concert, with important effects on growth control and body composition. While acting synergistically on bone, GH and IGF-1 have opposing effects on adipose tissue; GH is lipolytic while 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 growth hormone deficiency (GHD) treatment consists of daily subcutaneous GH injections of which there are many products available.

In the past, children with GHD who started daily GH replacement were expected to achieve normal adult height. However, outcomes have not matched expectations; most GHD children 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 pediatrics patients (and their parents) and denial and peer pressure among adolescent patients (3,4). Non-adherence also increases with time, thus impairing therapeutic response (5,6). Thus, optimizing patient adherence is critical as well as age of diagnosis and GH initiation.

The burdensome nature of a daily GH injectable makes a once-a-week, long-acting formulation attractive. Ideally, such a long-acting product would have similar safety, efficacy, and immunogenicity profiles compared to existing daily options, which may 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 at developing long-acting GH formulations. TransCon GH is a sustained-release inactive prodrug consisting of a parent drug, GH, transiently bound to methoxypolyethylene glycol molecule (mPEG) via a proprietary linker.

The inert mPEG acts as a carrier, extending GH circulation time in the body through a shielding effect that minimizes renal excretion and receptor binding (Figure 1).

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

The purpose of this investigation was to compare the pharmacokinetics (PK), pharmacodynamics (PD), 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 to daily Genotropin. 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 was obtained as well as signed informed consent from subject parent(s)/legal guardian(s). 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 based on auxological and biological criteria were enrolled. Auxological criteria for GHD diagnosis included short stature [height defined as 2.0 standard deviations (SD) 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 (based on 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 (with the second test 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, psychosocial dwarfism, idiopathic (or other causes of) short stature, a cranial tumor on MRI of the head, GHD secondary to malignancy, abnormal fundoscopy, abnormal SHOX 1 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 (Week 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 based on Tanner stages. Select laboratory tests were also drawn, including lipids, glucose, HbA1c, insulin, hormones, urinalysis, hematology, and chemistry. Subsequent visits included a physical examination, ECG, and repeat laboratory tests.

Eligible subjects were randomized to receive one of 3 subcutaneous doses of TransCon GH (ACP-001), ie, 0.14, 0.21, or 0.30 mg GH/kg/week (Cohort 1 to 3), or daily administered Genotropin 0.03 mg GH/kg/day (Cohort 4; equivalent to TransCon GH 0.21 mg GH/kg/week)

for 26 weeks. Study drug was administered based on the subject's weight measured prior to dosing during Week 1 and, if necessary, adjusted based on weight prior to dosing during Week 13.

Pharmacokinetics, Pharmacodynamics, Safety and Efficacy Assessments

Blood samples for PK and PD profiling were drawn at baseline and up to 168 hours post-dose during Week 1 and 13. Further 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 ELISA assay (Celerion Inc., Lincoln, NE, USA) while 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 SDS calculations were based on gender- 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 concentration post-dose. Area under the curve (AUC) for TransCon GH-treated subjects was calculated based on drug concentration at time 0 to 168 hours post-dose using the linear trapezoidal rule, with both uncorrected and baseline (pre-dose Week 1) corrected AUCs computed. AUC for Genotropin-treated subjects was calculated based on drug concentration at time 0 to 24 hours post-dose multiplied by 7 to be comparable to TransCon GH. For PD, 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 PK.

To ensure that GH and IGF-1 levels at baseline did not impact PK and PD calculations, post-treatment 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 adverse events (SAEs), 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 based on the Wong-Baker FACES Pain Rating Scale (10); results were included if the pain was over 3 and/or of a duration greater than 15 minutes. Injection site reactions were assessed on a scale of 0 to 3 based on 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 Limited, Abingdon, UK). Serum samples confirmed positive for anti-GH binding antibodies were assessed for anti-GH neutralizing antibody activity.

Statistical Analysis

Demographics 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/year) extrapolated. BMI SDS was calculated using Growth Analyser Research Calculation Tools version 4.0.30 (Rotterdam, The Netherlands). Analysis of covariance for Weeks 13 and 26 endpoints, 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 study drug were calculated. If a subject experienced more than one adverse event for the same period, only the adverse event 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 randomized. Two subjects withdrew after randomization but before first dosing and were thus excluded from further analyses. The remaining fifty-three subjects were randomized to four groups. Cohort 1 (n=12) received TransCon GH 0.14 mg/kg/week. Cohort 2 (n=14) received TransCon GH 0.21 mg/kg/week. Cohort 3 (n=14) received TransCon GH 0.30 mg/kg/week. Cohort 4 (n=13) received Genotropin 0.03 mg/kg/day (equivalent to TransCon GH 0.21 mg/kg/week).

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

Pharmacokinetics

The mean GH serum concentration profiles following subcutaneous administration of TransCon GH in Week 13 are presented in Figure 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 significant accumulation. Median GH T_{max} was 12 to 48 hours, a delayed T_{max} compared to Genotropin administration (Figure 3). GH exposure (C_{max} and AUC) following administration of TransCon GH or Genotropin at comparable weekly doses was similar.

Pharmacodynamics

Mean IGF-1 SDS at study baseline was approximately 2 SDS below predicted for age and sex in Cohorts 1 to 3 (Table 1). Following TransCon GH treatment, mean IGF-1 levels and IGF-1 SDS 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. Pre-dose (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 pre-dose levels attained from Week 13 onward (Figure 4). At Week 13, a dose-response was evident in absolute baseline corrected data, with IGF-1 SDS increasing into the normal range (-1.0 to +2.0 SDS) on all three doses of TransCon GH.

Individual IGF-1 SDS were below 2.0 for all Cohort 1 subjects throughout the study. Two subjects in Cohort 2 had IGF-1 SDS excursions above 2.0 during Week 13. Four subjects (one in Week 1 and three in Week 13) in Cohort 3 had IGF-1 SDS above 2.0. One additional subject in Cohort 3 had an IGF-1 SDS excursion above 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 SDS below 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 to 13.9

cm/year (Figure 5). Mean annualized HV was 11.6 cm/year for daily Genotropin compared to 12.9 cm/year at the equivalent weekly TransCon GH dose of 0.21 mg/kg/week. At the end of 26 weeks, the minimum annualized HV of 6.42 cm/year occurred at the lowest TransCon GH dose (Cohort 1) compared to 6.22 cm/year in Genotropin while the maximum annualized HV of 22.00 cm/year occurred at the highest TransCon GH dose (Cohort 3) compared to 19.25 cm/year in Genotropin. However, the differences across the four cohorts were not statistically significant. Delta height SDS increased from 0.7 to 0.9 in the three TransCon GH cohorts compared to 0.6 in the Genotropin cohort (Supplemental Figure 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 study drug. Supplemental Table 1 describes treatment-emergent adverse events occurring in more than 1 subject in any cohort.

One subject (1.9%) reported an SAE (inguinal hernia) assessed as mild in severity and considered unlikely to be related to study drug. Two subjects (3.8%) reported AEs with possible or probable relationships to study drug. The first subject, who received TransCon GH (Cohort 1), reported mild decreased appetite, nausea, and vomiting assessed as possibly related to study drug. The second subject, who received TransCon GH (Cohort 3), experienced mild iron deficiency anemia assessed as likely related to 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 daily somatropin's known safety profile.

TransCon GH and Genotropin tolerability were similar. Injection site reactions were reported by 25 subjects (7 in Cohort 1; 6 in Cohorts 2 to 4, respectively) collectively 141 times. Pain was most common, reported by 22 subjects (5 in Cohorts 1 and 2, respectively; 6 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 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 (1/40; 2.5%) receiving TransCon GH (Cohort 1) developed a treatment-emergent, anti-GH immune response initially detected at Week 13. Titration at Week 26 indicated the presence of very low titers of non-neutralizing anti-GH binding antibodies that did not appear to impact 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 out 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 7 days, was within physiological range and comparable to a weekly cumulative dose of daily Genotropin, interesting from both a safety and efficacy consideration. IGF-1 changes demonstrated a dose-response relationship to TransCon GH while IGF-1 SDS of all three TransCon GH doses normalized. Mean annualized HV ranged from 11.9 cm to 13.9 cm/year and compared favorably to 11.6 cm/year for daily Genotropin. Adverse events 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 daily GH without lipoatrophy or nodule formation seen. No neutralizing anti-GH binding antibodies were detected. The mean BMI SDS was stable across three TransCon GH cohorts as expected compared to daily GH.

Depending on methodology used, the prevalence of daily GH non-adherence ranges from 5 to 82% (3). A study in New Zealand by Cutfield et al demonstrated that two-thirds of patients who missed one or more doses per week showed significantly reduced linear growth compared to compliant patients (6). Thus, short-acting daily GH products may be both safe and effective, but this is of little consolation when not taken as prescribed. It is well established that the simpler a regimen, the more likely a patient will adhere to it, making long-acting GH ideal for hormone deficient children and adolescents, a patient population subject to long-term daily GH injections. As such, 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, non-neutralizing 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 GH's lipolytic effect, GH replacement results in the reduction of fat mass, particularly in the abdomen (12). In our study, the mean BMI SDS across TransCon GH cohorts was stable compared to a moderate decrease in the Genotropin cohort, the latter in the setting of a slightly higher mean BMI at baseline. Given TransCon GH's mechanism of action of releasing free GH, with GH and IGF-1 levels comparable to Genotropin, careful BMI monitoring over a longer TransCon GH treatment period in a larger cohort of GHD subjects is warranted.

Besides cardiac inflammation, children with GHD also have reduced cardiac mass, impaired diastolic filling, and reduced left ventricular response, which may at least be partially reversed with GH (13). However, while GH deficiency is problematic, so is GH excess. High endogenous 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/day, ie, 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 acromegaly patients. Unlike some long-acting products associated with supraphysiological GH levels, TransCon GH administration leads to both GH and IGF-1 levels similar to daily GH at comparable weekly doses, the latter which has many years of safety data (16).

TransCon GH was effective, with subjects achieving comparable height and annualized HV to that of daily GH. At all three doses given for 26 weeks, TransCon GH also out-performed the mean HV of 9.2 centimeters in the first year observed among compliant (ie, 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 to daily 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, not surprising given similar GH and IGF-1 exposure compared to daily GH. Excursions above 2.0 IGF-1 SDS across cohorts were infrequent, 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 based on IGF-1 levels with the goal of maintaining the range under 2.0 SDS. It was only in Cohort 3, at the highest TransCon GH dosing, that IGF-1 greater than 3.0 SDS 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 found that 30% of patients who received daily GH conventionally dosed at 0.04 mg/kg/day (closest in dosing to TransCon GH Cohort 3 recipients) had IGF-1 levels above 2 SDS (20). Of note, rigorous IGF-1 measurements are critical to GH dose titration. Since 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 (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 with only forty subjects receiving TransCon GH. However, despite a widely divergent prevalence range of 1/3480 to 1/30,000 cited in the literature (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 mg to mg conversion similar to 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.

ACKNOWLEDGMENTS

We thank the subjects, their caregivers, the principal investigators, Barbara Bleher and Karin Heidmann for clinical trial management assistance, Eva Dam Christoffersen and David Gilfoyle for bioanalytics assistance, and Eva Mortensen and Kennett Sprogøe for editorial assistance with the manuscript.

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Evgenia Mikhailova (Samara, Russia), Klaus Mohnike (Magdeburg, Germany), Voichita Mogos (Iasi, Romania), Agota Muzsnai (Budapest, Hungary), Aryaev Mykola (Odessa, Ukraine), Veronika Peretyatko (Donetsk, Ukraine), Valentina Peterkova (Moscow, Russia), Roland Pfäffle (Leipzig, Germany), Klaudziya Radziuk (Minsk, Belarus), Ganna Senatorova (Kharkiv, Ukraine), Ashraf El Sharkawy (El Mansoura, Egypt), Zeynep Siklar (Ankara, Turkey), Julia Skorodok (St. Petersburg, Russia), Jaroslav Škvor (Usti nad Labem, Czech Republic), Mieczyslaw Szalecki (Warsaw, Poland), Zsolt Vajda (Budapest, Hungary), Elpis Vlachopapadopoulou (Athens, Greece), Jacques Weill (Lille, France)

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CLINICAL TRIAL REGISTRATION NUMBER: NCT01947907

DISCLOSURE STATEMENT:

P.C, O.M., K.R., G.S., O.M., E.V., J.S., and V.P. were investigators for the study. P.C. is a consultant for and J.A.L. and M.B. are employees of Ascendis Pharma A/S.

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Figure 1: TransCon GH, a Sustained-Release Inactive Prodrug Consisting of Parent Drug, Unmodified GH, Transiently Bound to a Carrier, Methoxypolyethylene Glycol (mPEG), via a Proprietary Linker that is Auto-hydrolyzed Under Physiologic pH and Temperature

Figure 2: GH Serum Concentration (ng/mL), Arithmetic Means (+SD), Linear Scale, Untransformed Data, Following Weekly Administration of TransCon GH at Week 13

Figure 3: GH Serum Concentration (ng/mL), Arithmetic Means (+SEM), Linear Scale, Untransformed Data, Following Weekly Administration of TransCon GH (0 to 168 Hours) or Daily Administration of Genotropin (0 to 24 Hours) at Week 13

Figure 4: IGF-1 SDS, Arithmetic Means (+SD), Linear Scale, Untransformed Data, Following Weekly Administration of TransCon GH at Week 13

Figure 5: Annualized Height Velocity (Mean +SD) in 53 Subjects After 26 Weeks of TransCon GH vs. Genotropin Treatment

Table 1: Demographics and Baseline Characteristics at Visit 1 [ε]

	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, years (SD)	8.2 (2.9)	8.4 (2.1)	7.5 (2.8)	7.7 (2.5)
Mean bone age, years (SD)	5.2 (2.3)	6.5 (2.1)	4.7 (2.6)	4.9 (2.3)
Mean weight, kg (SD)	19.6 (5.6)	19.5 (4.9)	18.9 (6.6)	19.6 (6.3)
Mean height, cm (SD)	110.6 (16.3)	113.3 (11.6)	106.8 (16.0)	107.4 (15.0)
Mean height SDS (SD)	-3.1 (1.1)	-2.8 (0.4)	-3.2 (1.0)	-3.3 (1.1)
Mean BMI, kg/m^2 (SD)	15.8 (1.7)	15.0 (1.3)	16.1 (1.8)	16.6 (1.9)
Mean BMI SDS (SD)	-0.4 (1.1)	-0.9 (0.7)	-0.1 (1.0)	0.2 (0.8)
Mean GH stimulation test, ng/mL (SD)[¥]	5.1 (3.2)	5.2 (2.6)	4.4 (2.8)	5.2 (3.1)
Mean IGF-1, ng/mL (SD)[€]	80.8 (52.2)	80.3 (48.4)	62.5 (39.8)	53.8 (35.2)
Mean IGF-1 SDS (SD)[€]	-2.0 (0.7)	-2.0 (0.8)	-2.2 (0.7)	-2.5 (0.9)

[ε] Unless otherwise noted.
[¥] At screening.
[€] Uncorrected.