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MOD-4023 Phase 2 Study in GHD Children

Long-Acting CTP-Modified hGH (MOD-4023): Results of a Safety and Dose-Finding Study in GHD Children

Nataliya Zelinska¹, Violeta Iotova², Julia Skorodok³, Oleg Malievsky⁴, Valentina Peterkova⁵, Lubov Samsonova⁶, Ron G. Rosenfeld⁷, Zvi Zadik⁸, Michal Jaron-Mendelson⁹, Ronit Koren⁹, Leanne Amitzi⁹, Dmitri Raduk¹⁰, Oren HersHKovitz⁹, Gili Hart⁹

¹ Children Specialized Clinical Hospital, Kyev, Ukraine

² UMHAT, Varna, Bulgaria

³ St. Petersburg State Pediatric Medical Academy, St. Petersburg, Russia

⁴ Bashkir State Medical University, Ufa, Russia

⁵ Institute of Children's Endocrinology, Moscow, Russia

⁶ Russian Medical Academy of Postgraduate Education, Moscow, Russia

⁷ Oregon Health & Science University, Oregon, USA

⁸ Kaplan Medical Center, Rehovot, Israel

⁹ OPKO Biologics, Kiryat Gat, Israel

¹⁰ 2nd Children City Clinic, Minsk, Belarus

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Context: Daily injections are required for growth hormone replacement therapy, which may cause low compliance as a result of inconvenience and distress in patients.

Objective: CTP-modified human growth hormone (MOD-4023) is developed for once-a-week dosing regimen in GH-deficient (GHD) adults and children. The present trial was a safety and dose-finding study for weekly MOD-4023 in GHD children.

Design: a multi-center, open-label, randomized, controlled Phase 2 study in children with GHD, evaluating the safety, tolerability, PK/PD and efficacy of 3 different weekly MOD-4023 doses, compared to daily r-hGH.

Setting: The trial was conducted in 14 endocrinology centers in Europe.

Patients: 53 pre-pubertal children with GHD completed 12 months of treatment with either MOD-4023 (N=42) or r-hGH (N=11).

Interventions: CTP-modified hGH (MOD-4023) was administered weekly at a dose of either 0.25, 0.48, or 0.66 mg/kg/week, and compared to daily hGH at a dose of 0.24 mg/kg/week.

Results: MOD-4023 showed an estimated half-life approximately 5- to 10-fold longer when compared to daily r-hGH. IGF-I and IGF-BP-3 showed dose-dependent increase during MOD-4023 treatment. IGF-I SDS for MOD-4023 did not exceed +2. All MOD-4023 cohorts demonstrated adequate catch-up growth. The 0.66 mg/kg/week dose demonstrated efficacy closest to daily r-hGH. No serious adverse events were observed during MOD-4023 treatment, and its tolerability was consistent with known properties of r-hGH.

Conclusions: this study confirms the long-acting properties of MOD-4023 and shows a promising safety and tolerability profile. This provides support for initiation of a Phase 3 study in GHD children using a single weekly injection of MOD-4023.

PRECIS: A Phase 2 clinical study of long-acting, CTP-modified GH (MOD-4023) in GHD children using a once-weekly regimen confirms its safety profile and supports the initiation of a pivotal Phase 3 study.

List of Abbreviations

ADA, anti-drug antibodies; AE, adverse event; AUC, area under curve; BMI, body mass index; C_{max} , maximal concentration; CTP, C-terminal peptide; fT3, free thyroxine; fT4, free triiodothyronine; GCP, good clinical practice; GHD, growth hormone deficiency; HbA1c, hemoglobin A1c; hCG, human chorionic gonadotropin; hGHR, human growth hormone receptor; Ht, height; HV, height velocity; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding peptide 3; IGHD, isolated growth hormone deficiency; mAb, monoclonal antibody; MPHD, growth hormone deficiency associated with multiple deficiencies; NOAEL, no-observed-adverse-effect level; PD, pharmacodynamics; PK, pharmacokinetics; r-hGH, recombinant human growth hormone; SAE, serious adverse event; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; $T_{1/2}$, half-life; THSDS, target height standard deviation score; T_{max} , time of maximal concentration; TSH, thyroid-stimulating hormone.

Introduction

Human growth hormone (hGH), a 191-amino-acid pituitary protein, is an important endogenous factor responsible for skeletal growth and body mass. It stimulates the hepatic production and release of insulin-like growth factor I (IGF-I) into the systemic circulation, and is instrumental in the promotion of linear growth in children and in the control of metabolism and body composition in adults (1). Human growth hormone deficiency (GHD) is the consequence of low or absent secretion of growth hormone from the pituitary gland. In children, GHD results in inadequate circulating IGF-I levels and is manifested as abnormal linear growth (2). Children with complete absence of GH secretion are usually diagnosed before reaching the age of 3 years, whereas those with lesser degrees of deficiency are diagnosed at older ages.

Currently, daily GH supplementation is approved for the treatment of pediatric GH deficiency. However, despite ongoing improvements in injection device design, daily subcutaneous injections remain inconvenient, painful and distressing for many patients, leading to noncompliance, reduced efficacy, and increased healthcare costs. Compliance is a problem in up to 75% of teenagers, and is associated with reduced growth velocity (3-5). A long-acting form of GH has the potential to reduce discomfort and inconvenience, and can possibly provide substantial benefit by improving compliance and patients' quality of life (6). Currently, several approaches are being investigated as means to prolong the circulatory half-life of hGH (7-11).

MOD-4023 (CTP-modified hGH) is a long-acting recombinant human growth hormone intended for use as long-term treatment of children with growth failure due to inadequate endogenous growth hormone secretion, and as a replacement for endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult-onset. This long-acting formulation is expected to obviate the need for the numerous injections required in standard treatment of growth hormone deficiency. This technology is based on C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin (hCG) (12-14). As demonstrated in animal models (15), healthy subjects, and GHD adult patients (manuscript in preparation), MOD-4023 may have the potential to be injected once per week, resulting in similar clinical efficacy to daily injections of r-hGH. The present trial investigated MOD-4023 in a Phase 2 safety, tolerability, and dose-finding study in pre-pubertal pediatric patients with GHD. This was a randomized, active controlled study evaluating the safety,

tolerability and PK/PD profile of 3 different dosing regimens of weekly MOD-4023 compared to daily r-hGH (Genotropin).

Patients and Methods

Patients

The study was conducted at 14 sites in 7 countries. *Inclusion criteria* included: (i) prepubertal children aged ≥ 3 years and not above 10 years for girls or 11 years for boys, with either isolated GHD (IGHD), or GHD as part of multiple pituitary hormone deficiency (MPHD); (ii) confirmed diagnosis of GHD by two different GH provocation tests defined as a peak plasma GH level of ≤ 10 ng/ml using a validated assay (insulin tolerance / arginine / clonidine / glucagon (plus or without propranolol) / L-dopa plus propranolol); (iii) bone age no older than chronological age, and should not be greater than 9 years for girls and 10 years for boys; (iv) no prior exposure to any rhGH therapy; (v) impaired height and HV defined as height of at least 2.0 SD below the mean height for chronological age (CA) and gender (HT SDS ≤ -2.0) and annualized HV below the 25th percentile for CA (HV < -0.7 SDS) and gender, according to the standard growth charts of Prader et al. (16); (vi) BMI within ± 2 SD of mean BMI for the chronological age and sex according to the 2000 CDC standards (17); (vii) baseline IGF-I level at least 1 SD below the mean IGF-I level standardized for age and sex (IGF-I SDS ≤ -1.0); (viii) no signs/symptoms of intracranial hypertension; (ix) children with multiple hormonal deficiencies must have been on stable replacement therapy for at least 3 months (or 6 months for thyroid replacement therapy) prior to the first study drug administration; (x) normal 46 XX karyotype for girls; (xi) written informed consent of the parent or legal guardian of the patient and assent of the patient. *Exclusion criteria* included (i) past or present intracranial tumor growth; (ii) history of radiation therapy or chemotherapy; (iii) malnourished children, defined as serum albumin and iron below the lower limit of normal, and BMI < -2 SD for age and sex; (iv) psychosocial dwarfism; (v) children born small for gestational age (SGA), i.e. birth weight and/or birth length < 2 SD for gestational age; (vi) presence of anti-hGH antibodies at screening; (vii) any clinically significant abnormality likely to affect growth or the ability to evaluate growth; (viii) diabetes mellitus; (ix) impaired fasting sugar (fasting blood sugar > 110 mg/dl or 6.1 mmol/l after repeated blood analysis); (x) chromosomal abnormalities and medical syndromes (Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi Syndrome, Russell-Silver Syndrome, SHOX mutations/deletions and skeletal dysplasias), with the exception of septo-optic dysplasia; (xi) closed epiphyses; (xii) concomitant administration of other treatments that may have an effect on growth such as anabolic steroids and methylphenidate, with the exception of hormone replacement therapies (thyroxin, hydrocortisone, desmopressin [DDAVP]); (xiii) children requiring glucocorticoid therapy (e.g. asthma) that are taking a dose of greater than 400 μ g/d of inhaled budesonide or equivalents for longer than 1 month in a calendar year; (xiv) major medical conditions and/or presence of contraindication to rhGH treatment; (xv) known or suspected HIV-positive patient, or patient with advanced diseases such as AIDS or tuberculosis; (xvi) drug, substance, or alcohol abuse; (xvii) known hypersensitivity to the components of study medication; (xviii) other causes of short stature such as coeliac disease, hypothyroidism and rickets; (xix) the patient and/or the parent/legal guardian are likely to be non-compliant in respect to study conduct; (xx) participation in any other trial of an investigational agent within 30 days prior to screening.

Study design

This was a Phase 2 safety and dose finding study of different MOD-4023 dose levels (0.25, 0.48 and 0.66 mg/kg/week) compared to daily r-hGH therapy (0.24 mg/ml/week) in pre-pubertal growth hormone deficient children (ClinicalTrials.gov identifier NCT01592500). The patients were randomized in a 1:1:1:1 ratio to one of 3 the different MOD-4023 weekly dose cohorts or the Genotropin daily cohort. The randomization scheme ensured that the study population consisted of up to 40 patients with peak GH levels of ≤ 7 ng/mL (up to 10 patients per cohort) and up to 16 patients with peak GH level > 7 ng/mL and ≤ 10 ng/mL (up to 4 per cohort). The first 19 patients enrolled into the study were randomized via a web-based system (Target Health, New York, NY) using the following conditions: (i) chronological age (3-7, above 7); (ii) (height SDS – target height SDS) ≤ 3 and > 3 . Due to a programming error, this randomization resulted in an unexpected, unequal distribution of patients with regards to [height SDS – target height SDS] and peak plasma GH level. For the remaining patients enrolled in the study, randomization was performed manually using the same dynamic minimization rule while considering the following stratification factors: (i) stimulation tests peak plasma GH level: patients with peak GH level ≤ 7 ng/mL and patients with peak GH level > 7 ng/mL and ≤ 10 ng/mL; (ii) patients with peak plasma GH level ≤ 7 ng/mL were additionally stratified by age (patients ≤ 7 years and patients > 7 years). All dose levels tested are supported by a significant safety margin derived from the no observed adverse effect level (NOAEL) established in nonclinical toxicology studies (15). The low dose administered to Cohort 1 (0.25 mg MOD-4023 protein/kg/week) is a weekly molar equivalent to a standard daily dose of r-hGH of 0.025 mg/kg/day or 0.18 mg/kg/week. Cohort 2 was administered the weekly molar equivalent of the maximal recommended dose for GHD treatment (0.05 mg/kg/day, based on the Growth Hormone Society Consensus Guideline [18]). Cohort 3 was administered the weekly molar equivalent of the maximal approved dose for other pediatric indications (equivalent to 0.068 mg/kg/day). This study was carried out in compliance with the principles of Good Clinical Practice (GCP). The study protocol was reviewed and approved by the ethics committees at each study site. The study included a screening period and two active treatment periods (Figure 1). Following a 6-week screening period, eligible patients were randomized to one of 3 different MOD-4023 doses or to the standard daily r-hGH control group. The active treatment period lasted for 12 months, in which patients received weekly doses of MOD-4023 or daily doses of r-hGH. PK/PD, efficacy and safety assessments were performed throughout the period. Subsequent to the second administration of the targeted MOD-4023 dose, a sparse sampling approach was used for PK and PD sampling at T = 6 h up to 168 h. Patients allocated to the Genotropin cohort underwent limited PK/PD sampling after the 8th Genotropin dose (start of week 2 of dosing). Individual growth assessments for each patient were completed at the end of the period. In order to introduce naïve patients to the allocated MOD-4023 dose in a gradual manner, a stepwise dose increase was adopted. All patients randomized to receive one of the three MOD-4023 doses began treatment for 2 weeks with the low MOD-4023 dose (0.25 mg/kg). Based on the patient's dose allocation, this was followed by a dose increase to the next dose level every two weeks until the final allocated dose was reached.

IGF-I measurement

IGF-I was measured using the IDS-iSys chemiluminescence assay. Briefly, samples were incubated with an acidic solution to dissociate IGF-I from the binding proteins. This was followed by incubation with neutralisation buffer, biotinylated anti-IGF-I

monoclonal antibody (mAb), and acridinium-labelled anti-IGF-I mAb. Streptavidin-labelled magnetic particles were added and an additional incubation step followed. The particles were captured, washed, and trigger reagents are added. The light emitted by the acridinium label was directly proportional to the concentration of IGF-I in the original sample.

PK/PD analysis

PK/PD parameters were calculated using a population PK modelling approach, based on limited sampling in each patient. IGF-I SDS values were estimated using published reference tables (19). An empirical Bayesian estimation was performed in order to retrieve individual PK/PD model parameters. Individual concentration/time profiles were generated using rich sampling, and non-compartmental analysis was subsequently performed to estimate AUC and C_{\max} .

Efficacy evaluation

Height measurements were performed using a calibrated wall-mounted stadiometer. The arithmetic mean of 3 independent readings were obtained at each visit. The means, standard deviations (SD) of height, HV and HV SDS were derived from the standards of Prader et al. (16).

Safety evaluations

Safety evaluations included vital signs, injection-site reactions, immunogenic response and laboratory safety assessments. The latter included routine hematology and serum biochemistry, glucose and lipid parameters, as well as hormonal (thyroid and adrenal) status evaluation. For antibody assessments, qualitative validated methods were used to detect whether binding and/or neutralizing antibodies developed following once-weekly administration of MOD-4023 compared to daily r-hGH treatment. Serum samples for immunogenicity analysis were collected at pre-dose, and after 6 and 12 months of MOD-4023 / hGH treatment, using the anti-drug-antibodies (ADA) and neutralizing Ab methods for detection. Each sample was analyzed in screen format. Samples reactive for anti-MOD-4023 antibodies were confirmed for MOD-4023 specificity. Samples confirmed positive for anti-MOD-4023 binding antibodies were titered and analyzed for hGH and CTP specificity, as well as for anti-MOD-4023 and anti-hGH neutralizing activity using a cell-based assay. The assay is based on the ability of hGH/MOD-4023 to induce cell proliferation by binding to the human growth hormone receptor (hGHR) expressed on the surface of Human BaFB2B cells. The presence of anti-MOD-4023 neutralizing antibodies was determined qualitatively by measuring the inhibition of the GH proliferative effect. A titration curve of anti MOD-4023 in 2% normal pooled human serum at specific concentrations and tested samples was pre-incubated with fixed concentration of MOD-4023 (25 ng/ml) at room temperature. The cells were subsequently added and incubated for 18 ± 2 h at $37^{\circ}\text{C} + 5\% \text{CO}_2$. Following the incubation period, 30 μl of CellTiter96 AQueous One solution (Promega, Madison, WI) was added and incubated. The optical density at 490 nm is proportional to the number of living cells and inversely proportional to the amount of neutralizing antibodies.

Results

Patient disposition and characteristics

A total of 54 pre-pubertal children with either isolated GHD, or GHD as a part of multiple pituitary hormone deficiency, were enrolled in the study. One patient was enrolled into the study but discontinued prior to receiving any treatment; 53 children

completed 12 months of treatment with either MOD-4023 (N=42) or r-hGH (Genotropin; N=11). One patient was enrolled but misdiagnosed as GHD and therefore was excluded from the per-protocol efficacy analysis but was included in the safety and PK and PD analysis. Despite the limited sample size in each cohort, the baseline characteristics of the patients completing 12 months of treatment were well-balanced among the four cohorts (Table 1).

Pharmacokinetics

In order to evaluate the PK/PD profile of MOD-4023, a population-based PK/PD analysis was conducted. In addition, a naïve-pooled approach was used to estimate mean PK parameters (Table 2, Figure 2A and 2B). MOD-4023 showed an estimated half-life approximately 5- to 10-fold longer when compared to daily r-hGH. T_{max} was estimated to be at 12 hours for MOD-4023, as opposed to 2 hours for the daily Genotropin comparator arm, reaching trough levels by 168 hours. MOD-4023 AUC increased in a proportional manner to the dose. The serum level of MOD-4023 administered weekly reached steady-state levels after 7-10 weeks, without an increase in plasma levels (data not shown).

Pharmacodynamics

In terms of weekly trend, IGF-I was found to increase in a dose-dependent manner during treatment with MOD-4023 (calculated as change from baseline values and shown in Figure 2C). In addition, the calculated IGF-I SDS values for the MOD-4023 cohorts were shown to be within the normal range without exceeding +2 SDS (with the exception of one patient from the 0.66 mg/kg/week cohort who showed a transient slight increase of IGF-I SDS > +2) for most of the study period, based on sampling of patients at 48-72 hours post MOD-4023 dosing (Figure 2D). The IGF-I SDS profile for Cohort 1 (0.25 mg/kg/week) decreased during the second half of the week, and reached a mean value of approximately -2 SDS.

IGF-I SDS levels continued to increase gradually in a dose-dependent manner during 12 months of the study without reaching excessive IGF-I values for all but one patient (transiently) (Figure 2E and 2F). For most of the analysis period IGF-I SDS was below +2 SDS. Both 0.48 and 0.66 mg/kg/week cohorts reached a SDS of 0-0.5, comparable to that of the daily hGH group. A single exception was observed of a single patient in the 0.66 mg/kg/week group, who had an IGF-I level slightly higher than +2 SDS but did not exceed +2.5 SDS. These IGF-I levels were maintained when the dose was reduced to 0.48 mg/kg/week, confirming it as a patient-specific idiosyncrasy.

IGFBP-3 also increased in a dose-dependent manner upon MOD-4023 administration, reaching steady-state values around week 15 (see Supplementary Figure 1). To evaluate the long-term cumulative effect of weekly administration of MOD-4023, serum levels of IGF-I and IGFBP-3 were measured in blood samples obtained prior to the next weekly dosing and considered as the trough level of MOD-4023. The change in IGF-I serum levels and SDS, as well as IGFBP-3 serum levels from pre-treatment levels, demonstrated a slight dose-dependent increase from baseline (data not shown).

Efficacy evaluation

The annualized efficacy data for the four treatment groups are presented in Figure 3 for patients completing 12 months of treatment (n=52). The mean HV in the three MOD-4023 randomized dose groups and the daily GH group are presented in Figure 3A. During the first 12 months of treatment, catch-up growth (compared with the normal population) occurred in all four groups. Among the three dose cohorts of

patients treated with MOD-4023, the mean growth rate was lowest in the 0.25 mg/kg/wk MOD-4023 dose group (10.4 cm/year), and highest in the 0.66 mg/kg/wk MOD-4023 dose group (11.93 cm/year). The two dose groups of 0.25 and 0.48 mg/kg/week MOD-4023 demonstrated reduced mean annualized HV (10.4 ± 2.6 [range 6.2-14.4] and 11.0 ± 2.3 [range 6.5-14.5] cm/year, respectively) compared to daily Genotropin (12.5 ± 2.1 cm/year; range 9.2-16.0 cm/year), while the 0.66 mg/kg/week dose group showed a more pronounced response (11.9 ± 3.5 cm/year; range 6.4-18.3 cm/year), comparable to that of the daily hGH. The mean HV SDS and mean delta Ht SDS following 12 months of treatment are presented in Figure 3B and 3C. The majority of the patients transitioned from a negative HV SDS (below the age-adjusted mean, and in several cases, severely below the mean) to a substantially positive SDS (above 0, and above the upper age-adjusted normal range). The difference in age-adjusted Ht SDS following 12 months of treatment are presented in Figure 3C. Most of the patients in the study demonstrated an improvement in height SDS compared to pre-treatment values following 12 months of treatment. The mean gain in MOD-4023 dose groups after 12 months of treatment ranged from 1.14 to 1.45 SDS. Only the high dose of MOD-4023 (0.66 mg/kg/week) demonstrated a gain in height SDS comparable to the active control group (1.45 vs. 1.54, respectively).

Safety

Summary of the adverse events (AEs) is provided in Table 3. Overall, 37 of 53 patients (69.8%) experienced a total of 145 AEs during the study (Table 3). Eight patients (72.7%) reported a total of 33 AEs during the reporting period with daily r-hGH, and there were no severe AEs and no serious adverse events (SAEs) during treatment with daily r-hGH for up to 12 months. Twenty-nine patients (69.0%) reported 112 AEs during treatment with MOD-4023, with no severe AEs and no SAEs. Of the reported AEs, none led to MOD-4023 or daily r-hGH treatment withdrawal. Nine patients (21.4%) reported AEs in Cohort 1, while 10 patients (23.8%) reported AEs in both Cohort 2 and 3. Most patients reported little injection site pain (score of 2-3 out of 5), with the exception of one patient (0.66 mg/kg/wk MOD-4023 dose group) who experienced severe pain for 4 days.

No significant findings attributed to MOD-4023 were observed in glucose metabolism (glucose, HbA1c and insulin); the single case of impaired fasting glucose (0.25 mg/kg/week cohort) was mild and clinically insignificant. No adverse effects attributed to MOD-4023 were observed in TSH, fT4, fT3 and cortisol levels. The majority of mean blood chemistry values were within normal limits, with the exception of relative eosinophil and relative lymphocyte levels, which were also high at screening. The immunogenicity data showed low titers of non-neutralizing anti-MOD-4023 antibodies. Overall ADA incidence was similar for the study drug and the control group. For MOD-4023 the incidence rate was 11.9% (5/42; 3 patients in the 0.48 mg/kg/week cohort [20.0%] and 2 in the 0.66 mg/kg/week cohort [14.3%]), and 9.1% (1/11) for Genotropin. No anti-CTP antibodies were observed. No antibody-related AEs were reported during the study.

Discussion

This manuscript presents 12-month efficacy, safety and tolerability results of OPKO's Phase 2 clinical trial in pre-pubertal children with GHD. This study is the most recent stage in the clinical development of MOD-4023, a long-acting hGH utilizing OPKO's unique and versatile CTP technology. Fusing the protein to CTP enables the elongation of the protein's half-life using a naturally occurring human peptide that

also significantly reduces the risk of an adverse immune response compared to other long acting preparations currently in development. MOD-4023 was shown previously to have a favorable safety and tolerability profile in both a Phase 1 study in healthy adults and in a once-weekly dosing regimen in a Phase 2 trial in GHD adults (20). The present study showed that the estimated half-life of MOD-4023 administered weekly was longer than that of daily r-hGH. The latter's PK profile and $T_{1/2}$ are in line with daily r-hGH profiles reported in the literature (21). The variability observed in respect to MOD-4023 exposure is predominantly related to intra-patient variability and the small number of patients per cohort.

IGF-I, a validated surrogate marker for hGH activity (19, 22) increased in response to treatment with MOD-4023 (in line with the anticipated response for daily GH, as reported in the past by Péter et al. [21]). IGF-I SDS values did not exceed the normal range for most of the study, except transiently in rare situations. The rapid drop in IGF-I SDS values for Cohort 1 (0.25 mg/kg/week) during the second part of the week to a sub-optimal mean value suggests that this dose might not provide an optimal weekly IGF-I profile during long-term MOD-4023 therapy. In general, IGF-I SDS values showed an upward trend throughout the study. The daily r-hGH comparator Genotropin also demonstrated an elevation in IGF-I SDS values, in line with previous reports in the literature (23, 24), and showed a similar trend to that observed in the two highest dose cohorts of MOD-4023. This comparable outcome can be explained by the fairly small increase (~30%) in the MOD-4023 dose between the 0.48 and 0.66 mg/kg/week cohorts, as opposed to a larger increment of almost 50% in the MOD-4023 dose in the 0.25 mg/kg/week cohort as compared to the 0.48 mg/kg/week cohort. A significant effect on IGF-I might be less pronounced as the increment in MOD-4023 is reduced, in line with Cohen et al., who demonstrated a modest increase in IGF-I when increasing the dose by 100% (24).

MOD-4023 trough levels measured on the 23rd week of treatment further confirmed that residual MOD-4023 levels at all three doses were very low to undetectable (data not shown).

As shown in previous pre-clinical studies, the specific activity of MOD-4023 is lower than that of r-hGH (15). This indicates that comparison of the biological/physiological effect of weekly MOD-4023 and daily r-hGH is more appropriate than a direct molar comparison. In terms of efficacy, all cohorts demonstrated adequate catch-up growth after 12 months of MOD-4023 treatment in comparison to the normal age-adjusted population. All patients responded very well to treatment, as reflected by the 12-month increase in HV SDS and Δ Ht SDS values, and in most cases, the growth rate was accelerated relative to the normal age group. The 0.66 mg/kg/week dose demonstrated the best annualized HV, HV SDS and Δ Ht SDS, with values that were the closest to the daily r-hGH results. With respect to correlation between the IGF-I SDS profile and annual HV, although IGF-I increases with GH treatment, there is no direct or validated correlation between the IGF-I and annual HV (24). This suggest that although the level of IGF-I impacts growth, other parameters are affected by baseline characteristics, including genetic background (25, 26). Finally, it is well known that growth hormone might also have a direct impact on growth response, independently of IGF-I (27).

MOD-4023 was shown to be safe during treatment of up to 12 months, with no SAEs, and tolerability consistent with known properties of r-hGH products. No patients withdrew from the study due to an AE associated with the investigational product, indicating that MOD-4023 was well tolerated by all patients. There was no discernible trend of AE frequency with escalating doses of MOD-4023. Relatively

few AEs were attributed to MOD-4023 overall, and those that were attributed to MOD-4023 are of a similar nature and severity as those encountered with daily r-hGH products. One case of mild adrenal insufficiency and one case of moderate secondary adrenocortical insufficiency were assessed as being possibly related to study drug administration, since GH treatment may unmask previously undiagnosed or sub-clinical hypoadrenalism (28). During the first 12 months of the Phase 2 study in GHD pediatric population, in line with previous Phase 2 data in GHD adults, MOD-4023 demonstrated a promising immunogenic profile, with no detection of binding antibodies against the CTP moiety nor any neutralizing activity. Subjects that had developed antibodies against MOD-4023 demonstrated adequate annual HV and HV SDS ranges (data not shown), suggesting that the presence of ADA had no effect on MOD-4023 efficacy.

In conclusion, the present study confirms the long-acting properties of MOD-4023 and shows a promising 12-month safety and tolerability profile for this novel compound. Taken together, these provide support for the initiation of a Phase 3 study in GHD children using a single weekly injection of MOD-4023. Based on the 12-month data presented here, it is most likely that a MOD-4023 dose of 0.66 mg/kg/week will provide an annualized HV comparable to daily hGH at a dose of 34 µg/kg/day. These doses will therefore serve as a basis for the upcoming Phase 3 study.

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Corresponding author and person to whom reprint requests should be addressed: Gili Hart, PhD, OPKO Biologics, 16 Ashlagan St., Kiryat Gat, Israel, Phone: +972-8-9300051, Fax: +972-8-9300091, e-mail: ghart@opko.com

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References

1. Murray PG, Higham CE, Clayton PE. The hypothalamo-GH axis: the past 60 years. *J Endocrinol* 2015; 226:T123-140.
2. Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P, Sönksen PH, Tanaka T, Thorne M. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab* 1998; 83:382-395.
3. Høybye C, Cohen P, Hoffman AR, Ross R, Biller BM, Christiansen JS; Growth Hormone Research Society. Status of long-acting-growth hormone preparations - 2015. *Growth Horm IGF Res* 2015; 25:201-206.
4. Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract* 2008; 14:143-154.
5. Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, Robinson E, Hofman PL. Non-compliance with growth hormone treatment in children is common and impairs linear growth. *PLoS ONE* 2011; 6:e16223.

6. Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BM, Boguszewski MC, Casanueva FF, Chanson P, Chatelain P, Choong CS, Clemmons DR, Cohen LE, Cohen P, Frystyk J, Grimberg A, Hasegawa Y, Haymond MW, Ho K, Hoffman AR, Holly JM, Horikawa R, Höybye C, Jorgensen JO, Johannsson G, Juul A, Katznelson L, Kopchick JJ, Lee KO, Lee KW, Luo X, Melmed S, Miller BS, Misra M, Popovic V, Rosenfeld RG, Ross J, Ross RJ, Saenger P, Strasburger CJ, Thorner MO, Werner H, Yuen K.. Growth Hormone Research Society Perspective on the Development of Long-Acting Growth Hormone Preparations. *Eur J Endocrinol* 2016; 174:C1-8.
7. Khadilkar V, Radjuk KA, Bolshova E, Khadgawat R, El Kholy M, Desai M, Peterkova V, Mericq V, Kratzsch J, Siepl EC, Martin D, Lopez P, Ji HJ, Bae YJ, Lee JH, Saenger PH. 24-month use of once-weekly GH, LB03002, in prepubertal children with GH deficiency. *J Clin Endocrinol Metab*. 2014; 99:126-132.
8. Cohen-Barak O, Sakov A, Rasamoeliso M, Bassan M, Brown K, Mendzelevski B, Spiegelstein O. Safety, pharmacokinetic and pharmacodynamic properties of TV-1106, a long-acting GH treatment for GH deficiency. *Eur J Endocrinol* 2015; 173:541-551.
9. Kim SJ, Kwak H-H, Cho SY, Sohn YB, Park SW, Huh R, et al. Pharmacokinetics, pharmacodynamics, and efficacy of a novel long-acting human growth hormone: Fc fusion protein. *Mol Pharm* 2015; 12:3759-3765.
10. Hou L, Chen ZH, Liu D, Cheng YG, Luo XP. Comparative pharmacokinetics and pharmacodynamics of a PEGylated recombinant human growth hormone and daily recombinant human growth hormone in growth hormone-deficient children. *Drug Des Devel Ther* 2016; 10:13-21.
11. Moore WV, Nguyen HJ, Kletter GB, Miller BS, Rogers D, Ng D, Moore JA, Humphriss E, Cleland JL, Bright GM. A randomized safety and efficacy study of somavaratan (VRS-317), a long-acting rhGH, in pediatric growth hormone deficiency. *J Clin Endocrinol Metab* 2016; 101:1091-1097.
12. Matzuk MM, Hsueh AJ, Lapolt P, Tsafiriri A, Keene JL, Boime I. The biological role of the carboxyl-terminal extension of human chorionic gonadotropin [corrected] beta-subunit. *Endocrinology* 1990; 126:376-383.
13. Fares FA, Sukanuma N, Nishimori K, LaPolt PS, Hsueh AJ, Boime I. Design of a long-acting follitropin agonist by fusing the C-terminal sequence of the chorionic gonadotropin beta subunit to the follitropin beta subunit. *Proc Natl Acad Sci USA* 1992; 89:4304-4308.
14. Calo D, Hart G, Hoffman M, Yagev Israeli L, Tzur Y, Binder L, Monahan P, Zakar M, Guy R, Felikman Y, Moschovich L, Bar-Ilan A, Hershkovitz O. Enhancing the longevity and in vivo potency of therapeutic proteins: the power of CTP. *Precis Med* 2015; 2:e989.
15. Hershkovitz O, Bar-Ilan A, Guy R, Felikman Y, Moschovich L, Hwa V, Rosenfeld RG, Fima E, Hart G. In vitro and in vivo characterization of MOD-4023, a long-acting carboxy-terminal peptide (CTP)-modified human growth hormone. *Mol Pharm* 2016; 13:631-639.
16. Prader A, Largo RH, Molinari L, Issler C. Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. *Helv Paediatr Acta Suppl* 1989; 52:1-125.
17. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. *Adv Data* 2000; 314:1-27.
18. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence:

summary statement of the GH Research Society. GH Research Society. *J Clin Endocrinol Metab.* 2000; 85:3990-3993.

19. Bidlingmaier M, Friedrich N, Emeny RT, Spranger J, Wolthers OD, Roswall J, Körner A, Obermayer-Pietsch B, Hübener C, Dahlgren J, Frystyk J, Pfeiffer AF, Doering A, Bielhuby M, Wallaschofski H, Arafat AM. Reference intervals for insulin-like growth factor-1 (IGF-I) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. *J Clin Endocrinol Metab* 2014; 99:1712-1721.
20. Strasburger CJ, Vanuga P, Payer J, Pfeifer M, Popović V, Bajnok L, Góth MI, Olšovská V, Trejbalová L, Vadasz J, Fima E, Koren R, Amitzi L, Bidlingmaier M, HersHKovitz O, Hart G, Biller BMK. MOD-4023, a long-acting carboxy-terminal peptide (CTP)-modified human growth hormone: results of a Phase 2 study in growth hormone-deficient adults. *Eur J Endocrinol* 2016; DOI: 10.1530/EJE-16-0748 [accepted preprint].
21. Péter F, Bidlingmaier M, Savoy C, Ji H-J, Saenger PH. Three-year efficacy and safety of LB03002, a once-weekly sustained-release growth hormone (GH) preparation, in prepubertal children with GH deficiency (GHD). *J Clin Endocrinol Metab* 2012; 97:400-407.
22. Bielhuby M, Zarkesh-Esfahani SH, Manolopoulou J, Wirthgen E, Walpurgis K, Toghiani Khorasgani M, Aghili ZS, Wilkinson IR, Hoeflich A, Thevis M, Ross RJ, Bidlingmaier M. Validation of serum IGF-I as a biomarker to monitor the bioactivity of exogenous growth hormone agonists and antagonists in rabbits. *Dis Model Mech* 2014; 7:1263-1273.
23. Peter F, Savoy C, Ji H-J, Juhasz M, Bidlingmaier M, Saenger P. Pharmacokinetic and pharmacodynamic profile of a new sustained-release GH formulation, LB03002, in children with GH deficiency. *Eur J Endocrinol* 2009; 160:349-355.
24. Cohen P, Germak J, Rogol AD, Weng W, Kappelgaard AM, Rosenfeld RG; American Norditropin Study Group. Variable degree of growth hormone (GH) and insulin-like growth factor (IGF) sensitivity in children with idiopathic short stature compared with GH-deficient patients: evidence from an IGF-based dosing study of short children. *J Clin Endocrinol Metab* 2010; 95:2089-2098.
25. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price DA. Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. KIGS International Board. Kabi Pharmacia International Growth Study. *J Clin Endocrinol Metab.* 1999; 84:1174-1183.
26. Ranke MB, Lindberg A, KIGS International Board. Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. *J Clin Endocrinol Metab.* 2010; 95:1229-1237.
27. Yakar S, Isaksson O. Regulation of skeletal growth and mineral acquisition by the GH/IGF-1 axis: Lessons from mouse models. *Growth Horm IGF Res.* 2016; 28:26-42.
28. Giavoli C, Libé R, Corbetta S, Ferrante E, Lania A, Arosio M, Spada A, Beck-Peccoz P. Effect of recombinant human growth hormone (GH) replacement on the hypothalamic-pituitary-adrenal axis in adult GH-deficient patients. *J Clin Endocrinol Metab.* 2004; 89:5397-5401.

Figure 1: Overview of Study Design Following a screening periods, patients were randomized to one of 3 MOD-4023 weekly dose cohorts (C1-C3) or to the standard daily r-hGH control cohort (C4). The patients were introduced to their allocated MOD-4023 dose using a stepwise dose increase every 2 weeks. The active treatment period lasted for a total of 12 months.

Figure 2: PK and PD Profiles of MOD-4023 Administered Weekly. The weekly plasma concentration-time profiles for weekly MOD-4023 and daily r-hGH are presented in panels A and B, respectively. MOD-4023 serum levels were measured at the final randomized dose (following the 2nd dose). r-hGH serum concentration was measured following 2 weeks of daily administration. At each time point, the mean values represent an average of 3-4 patients. Weekly trends of IGF-I levels are shown as mean change from baseline (C) and mean SDS (D). Panels E and F presents IGF-I serum levels and IGF-I SDS trends, respectively, for patients completing 12 months of treatment.

Figure 3: Efficacy of MOD-4023 in GHD Children following 12 Months of Treatment. Mean annualized HV (A), HV SDS (B) and Δ Ht SDS (C) of the three MOD-4023 dose groups (Cohorts 1-3) vs. daily r-hGH (Cohort 4). The error bars represent standard error.

Table 1: Demographics and Patient Disposition

Characteristic	Cohort 1	Cohort 2	Cohort 3	Cohort 4
	0.25 mg/kg/wk (N=13)	0.48 mg/kg/wk (N=15)	0.66 mg/kg/wk (N=14)	Genotropin (N=11)
Mean age	6.2 ± 2.2	5.8 ± 2.3	6.1 ± 2.2	5.7 ± 1.9
Minimum, maximum age	(4, 11)	(3, 10)	(3, 10)	(4, 9)
Male	10 (76.9%)	9 (60.0%)	9 (64.3%)	8 (72.7%)
Female	3 (23.1%)	6 (40.0%)	5 (35.7%)	3 (27.3%)
Caucasian	12 (92.3%)	14 (93.3%)	14 (100.0%)	10 (90.9%)
Total Non-Caucasian	1 (7.7%)	0 (0)	0 (0)	1 (9.1%)
Patients with IGHD	8 (61.5%)	11 (73.3%)	11 (78.5%)	9 (81.8%)
Patients with MPHD	5 (38.5%)	4 (26.7%)	3 (21.5%)	2 (18.2%)
Ht SDS	-3.64 ± 0.97	-3.72 ± 0.87	-4.21 ± 1.45	-4.22 ± 1.58
Ht SDS – THSDS	-3.22 ± 0.95	-3.00 ± 0.70	-3.36 ± 1.54	-3.68 ± 1.70
HV SDS	-2.93 ± 1.42	-2.68 ± 1.00	-3.01 ± 1.42	-3.29 ± 1.91
Peak GH (ng/mL)	3.93 ± 3.15	4.13 ± 2.64	3.97 ± 2.97	3.82 ± 2.78
IGF-I (ng/mL)	-2.21 ± 0.84	-2.13 ± 0.77	-1.97 ± 0.83	-2.15 ± 0.94

Table 2: Mean PK Parameters for MOD-4023 and r-hGH

Parameter	Weekly MOD-4023			Daily r-HGH
	0.25 mg/kg/week (N=13)	0.48 mg/kg/week (N=15)	0.66 mg/kg/week (N=13)	0.24 mg/kg/week (N=11)
t _{1/2} (hr)	36.1	18.3	22.4	3.5
T _{max} (hr)	12	12	6	2
AUC _{0-∞} (ng/mL*hr)	10930.3	20491.6	28084.9	135.7
C _{max} (ng/mL)	460	810.2	1150.9	17.3

Table 3: Summary of Adverse Events Possibly, Probably or Definitely Related to MOD-4023 Treatment

	MOD-4023 treatment				r-hGH treatment
	Cohort 1	Cohort 2	Cohort 3	Total (1-3)	Cohort 4
No. of patients	13	15	14	42	11
No. of patients with any AEs	9	10	10	29	8
No. of AEs possibly, probably or definitely related to MOD-4023 treatment	2	2	5	9	0
Anemia	0	2	2	4	0
Adrenal insufficiency	1	0	0	1	0
Secondary adrenocortical insufficiency	0	1	0	1	0
Erythema	0	0	1	1	0
Swelling	0	0	1	1	0
Hematoma	0	0	1	1	0
Impaired fasting glucose	1	0	0	1	0
Hematuria	0	0	1	1	0

ADVANCE ARTICLE





