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Pharmacokinetics, Pharmacodynamics, and Safety of a Long-Acting Human Growth Hormone (MOD-4023) in Healthy Japanese and Caucasian Adults

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Abstract

Daily injections of growth hormone (GH) as replacement therapy in GH-deficient (GHD) patients may cause poor compliance and inconvenience. C-terminal peptide–modified human GH (MOD-4023) has been developed for once-weekly administration in GHD adults and children. In the present study, the pharmacokinetics (PK) and pharmacodynamics (PD) of a single subcutaneous dose of MOD-4023 were evaluated in healthy Caucasian and Japanese adults, using a phase 1 double-blind, vehicle-controlled, randomized study design. The study was conducted in 42 healthy Japanese (n = 21) and Caucasian (n = 21) men receiving either MOD-4023 at a dose of 2.5, 7.5, or 15 mg or vehicle. In the 2.5- and 7.5-mg cohorts, no differences in mean MOD-4023 serum concentration were found between Japanese and Caucasian subjects. A comparison of PK parameters in the 15-mg group suggests a slower absorption rate of MOD-4023 in Japanese subjects. PD analysis showed no apparent differences in IGF-1 and IGFBP-3 plasma concentrations between the Japanese and Caucasian subjects and indicated that a dose of 15 mg achieved the maximal effect in both ethnic groups. MOD-4023 demonstrated a favorable safety profile and local tolerance following single-dose subcutaneous administration. This study provides additional support for the development of MOD-4023 as a long-acting human growth hormone formulation for once-weekly administration.

Keywords

insulin-like growth factor 1 (IGF-1), growth hormone deficiency (GHD), weekly GH, Japanese, MOD-4023

Growth hormone deficiency (GHD) leads to inadequate levels of circulating insulin-like growth factor-1 (IGF-1) and, in children, to abnormal linear growth. GHD in adults results in decreased lean body mass, increased fat mass, weakness, reductions in exercise capacity, muscle mass/strength, cardiac performance, bone density, and neuropsychological disturbances.[1,2] Growth hormone (GH) replacement therapy has been the standard of care for more than 50 years in tens of thousands of patients and has proved to be safe and effective.[3,4] The majority of currently available human growth hormone (hGH) products require daily subcutaneous injections to maintain hGH blood levels within the effective therapeutic window. The main therapeutic aim of growth hormone treatment in children with GHD is to enable short children to achieve normal height, whereas the goal of replacement therapy in adults is to correct the metabolic, functional, and psychological abnormalities associated with adult GHD. The recommended starting dose of GH in young men and women is 0.2 and 0.3 mg/day, respectively (or 0.1 mg/day in older individuals), and that the dose be titrated according to IGF-1 levels. Determination of dose according to body weight is not recommended because of high variability between individuals.[3]

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MOD-4023 is a long-acting recombinant hGH fused to the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin[5–7] and developed for subcutaneous administration. In vitro and in vivo studies have shown MOD-4023 to be safe and well tolerated, with a suitable pharmacokinetic (PK) profile and biological activity to support a weekly-dosing regimen.[8] This regimen was confirmed in subsequent clinical trials in GHD adults[9] and in GHD children.[10,11] A phase 3 trial in GHD adults has been recently completed, and a pivotal phase 3 study in GHD children is currently under way.

The difference in mean normal height between Japanese and Caucasian individuals can be affected by multiple factors, including genetics and ethnic background.[12] Ethnicity-related differences in PK and pharmacodynamics (PD) may also be a potential cause of the variability in drug response, which could lead to differences in dosing.[13] Ethnic differences may be ascribed to differences in diet and concomitant medication, as well as genetic differences in metabolism.[14] Therefore, the development of MOD-4023 as a novel hGH formulation with elongated plasma half-life warrants the comparison of the PK/PD profile of the drug in Caucasian and Asian populations. The purpose of the current phase 1 study was to evaluate the safety and PK profile of 3 doses of MOD-4023 in healthy Caucasian and Japanese adult male subjects. The study was conducted at a phase 1 unit in the United States in a randomized, double-blind, vehicle-controlled, parallel-group design.

Subjects and Methods

Subjects

The study was conducted at a single center in the United States (WCCT Global, Cypress, California) and included 42 healthy Caucasian and first-generation Japanese adult men. Signed informed consent was obtained from all subjects prior to screening. Inclusion criteria included body mass index of 18–30 kg/m^2 and body weight > 55 kg; nonsmokers or light smokers (less than 10 cigarettes per day); negative HIV, hepatitis B, and hepatitis C serology at screening; and no history of alcohol or drug abuse within 1 year of screening. Exclusion criteria included history of clinically significant disorders, including diabetes mellitus/prediabetes; known allergies to GH or vehicle; abnormal diet during the 4 weeks prior to study drug administration; recent significant changes in body weight; use of medications within 14 days prior to study drug administration; receipt of vaccinations within 4 weeks prior to study drug administration; blood donation or receipt of blood/plasma derivatives in the month preceding signing of the consent form; and administration of systemic corticosteroids (other than in replacement doses) within 3 months prior to study drug administration.

Study Design

This was a phase 1 randomized, double blind, vehicle-controlled, single-dose, 3-dose-level parallel-group study in healthy Caucasian and Japanese adult male subjects. A single dose of MOD-4023 was administered at 1 of 3 dose levels: 2.5 mg (0.13 mL), 7.5 mg (0.38 mL), and 15 mg (0.75 mL). The dose selection for this study was based on previous nonclinical and clinical studies.[8,9] The data obtained from a phase 1 study in healthy adult men,[7] a phase 2 study in adults with GHD,[9] and a phase 2 study in GHD children[10] provided a favorable safety profile and confirmed the adequacy of a weekly regimen of MOD-4023, as reflected by normalizing IGF-1 standard deviation score (SDS) values. The average effective dose that was shown to maintain adult men with GHD within the IGF-1 SDS normal range was 2.5 mg. On the basis of these results and assuming a similar response in the Japanese population, the lowest dose in the present study (2.5 mg) was also used as the initial dose in an ongoing phase 3 study in GHD adults, whereas the middle and high doses potentially provided 3- and 6-fold exposure margins, respectively, over the initial clinical dose.

Following a 4-week screening period, eligible male subjects were stratified by ethnic group and randomized to 1 of 6 groups, as shown in Figure 1. For each dose level, eligible subjects were randomly assigned in a 6:1 ratio to receive a single dose of MOD-4023 or placebo (vehicle). MOD-4023 was provided as a 20 mg/mL solution (having a net recombinant hGH content of 72.3%) in 10 mM sodium citrate, 147 mM sodium chloride, pH 6.4 (Rentschler Biotechnologie, Laupheim, Germany). The placebo comprised citrate buffer (10 mM sodium citrate, 147 mM sodium chloride). Allocation to the active or placebo group was double-blinded within each cohort; however, because of the difference in volume (0.13, 0.38, and 0.75 mL for the 2.5-, 7.5-, and 15-mg groups, respectively), allocation to the various doses was not blinded. On dosing day, each subject received a single subcutaneous injection of the study drug or placebo in the upper arm, thigh, or abdomen and was followed up for a month for safety monitoring. The total duration of subject participation in the study was up to 58 ± 2 days.

For the determination of MOD-4023 serum concentrations, a total of 15 blood samples (8.5 mL per sample) were drawn from each subject at the following points: predose (up to 60 minutes before injection) and 2, 4, 6, 8 hours (all ±5 minutes), 10, 12 hours (both ±15 minutes), 18 hours (±30 minutes), 24 hours (±1 hour), 36 hours (±1.5 hours), 48 hours (±2 hours), 72 hours (±2 hours), 96 hours (±2 hours), 168 hours

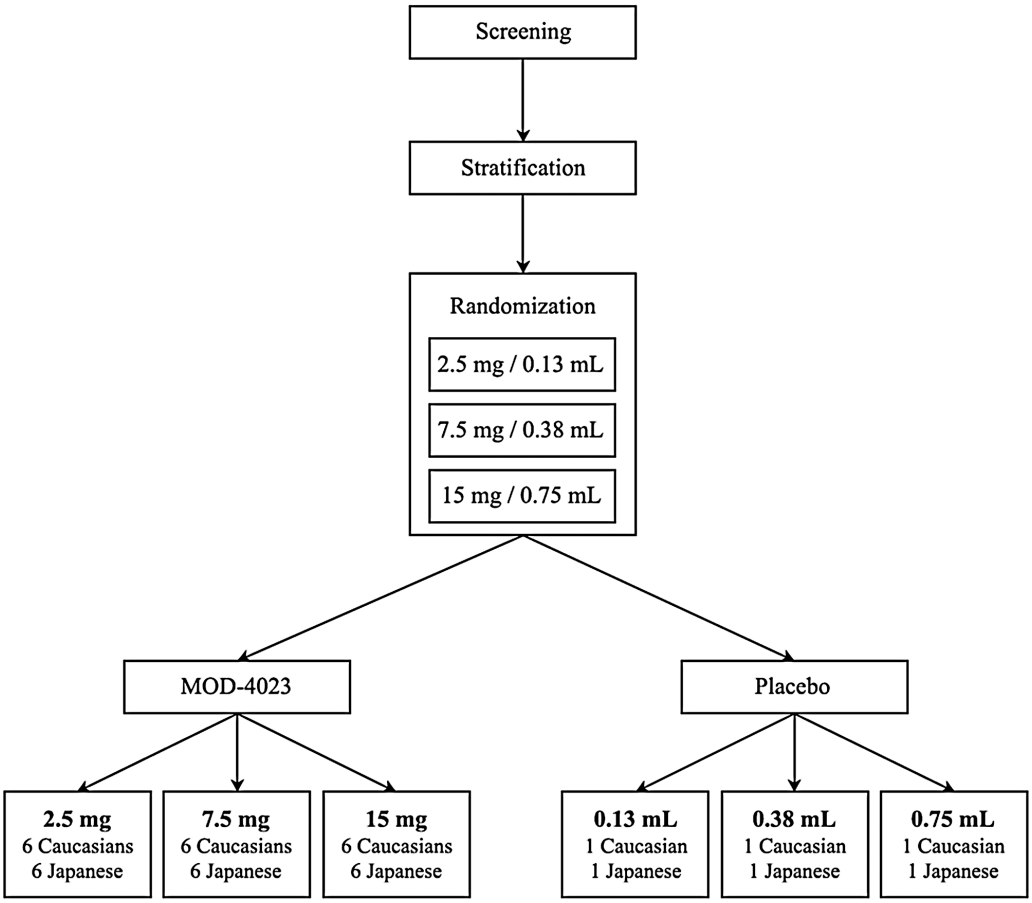

Figure 1. Overall study design. The study was a randomized, vehicle-controlled, single-dose, 3-dose-level parallel-group clinical trial. Following a 4-week screening period, eligible male subjects were stratified by ethnic group and randomized to 1 of 6 groups. In each group, subjects were administered with a single subcutaneous dose of either MOD-4023 (2.5, 7.5, and 15 mg) or placebo (vehicle).

(±2 hours), and 336 hours (±24 hours) after injection. For the measurement of IGF-1 and IGF-binding protein 3 (IGFBP-3), blood samples (8.5 mL per sample) were drawn predose (up to 60 minutes before injection) and 6 hours (±5 minutes), 12 hours (±15 minutes), 24 hours (±1 hour), 48 hours (±2 hours), 72 hours (±2 hours), 96 hours (±2 hours), 168 hours (±2 hours), and 336 hours (±24 hours) postdose. All blood samples were stored at -20°C until analysis. The final protocol and informed consent documentation were reviewed and approved by the study's institutional review board (Aspire IRB, Santee, California).

PK/PD Analysis

Serum concentrations of MOD-4023 were measured using a validated quantitative electrochemiluminescent (ECL) technique by Intertek Pharmaceutical Services (San Diego, California). This method used a sandwich ECL assay format to measure the concentration of MOD-4023 in human serum. Standards, controls, and test samples containing MOD-4023 were incubated with biotinylated anti-hGH antibody immobilized on a streptavidin-coated 96-well plate (Meso Scale Diagnostics, Rockville, Maryland). After incubation, MOD-4023 was detected with Sulfo-Tag anti-CTP antibody, visualized with Read Buffer T (2×), and read on a Sector Imager 2400 (Meso Scale Diagnostics). The range of quantitation during sample analysis was 30–7200 pg/mL; with the minimum required dilution of 1:5, the lowest quantifiable sample concentration was 150 pg/mL. The mean intra- and interassay coefficient of variation (%CV) ranges were 6.3–12.4 and 6.0–11.1, respectively.

Noncompartmental analysis was used to calculate the pharmacokinetic parameters for MOD-4023 using PKSolver.[15] Only serum concentrations that were equal to or greater than the validated limit of quantitation (LOQ) for the assay (150 pg/mL) were used in the PK analyses. Serum concentrations < LOQ were taken as 0 for the calculation of the descriptive statistics for serum concentrations at each sampling time. For the PK analysis, serum concentrations < LOQ that occurred from predose to the first concentration ≥ LOQ were treated as 0, and those that occurred thereafter were treated

Table 1. Subject Demographics and Baseline Characteristics

		MOD-4023			
	Placebo (n = 6)	2.5 mg (n = 12)	7.5 mg (n = 12)	15 mg (n = 12)	All (n = 42)
Japanese subjects					
Age (years)					
Mean (SD)	30.3 (8.0)	34.8 (7.9)	34.0 (7.3)	37.2 (6.4)	34.6 (7.1)
Median (minimum–maximum)	31.0 (22.0–38.0)	36.0 (21.0–45.0)	32.0 (25.0–45.0)	38.5 (29.0–44.0)	35.0 (21.0–45.0)
Weight (kg)					
Mean (SD)	66.6 (8.0)	67.9 (6.6)	71.5 (8.9)	63.6 (5.1)	67.5 (7.3)
Median (minimum–maximum)	69.8 (57.5–72.6)	70.6 (57.4–74.6)	72.3 (59.6–82.2)	64.6 (57.3–71.0)	67.3 (57.3–82.3)
Height (cm)					
Mean (SD)	163 (8)	175 (2)	173 (7)	172 (6)	172 (6)
Minimum–maximum	156–172	173–179	164–180	165–179	156–180
BMI (kg/m^2)					
Mean (SD)	24.8 (2.1)	22.3 (2.2)	23.9 (1.5)	21.3 (1.0)	22.8 (2.1)
Minimum–maximum	23.6–27.3	18.5–24.1	22.0–25.4	19.9–22.7	18.5–27.3
Caucasian subjects					
Age (years)					
Mean (SD)	34.0 (5.6)	27.7 (4.1)	32.2 (6.7)	27.2 (3.4)	29.7 (5.4)
Median (minimum–maximum)	35.0 (28.0–39.0)	28.0 (22.0–34.0)	31.5 (22.0–40.0)	27.0 (22.0–32.0)	29.0 (22.0–40.0)
Weight (kg)					
Mean (SD)	77.2 (5.5)	80.5 (10.4)	81.7 (7.3)	80.9 (6.6)	80.5 (7.5)
Median (minimum–maximum)	75.1 (73.1–83.5)	82.1 (61.8–90.7)	82.8 (73.3–92.2)	79.9 (75.0–91.3)	82.0 (61.8–92.2)
Height (cm)					
Mean (SD)	182 (2)	180 (6)	175 (5)	181 (3)	179 (5)
Minimum–maximum	181–185	169–186	167–182	178–187	167–187
Body mass index (kg/m^2)					
Mean (SD)	23.2 (1.1)	25.0 (3.5)	26.6 (1.7)	24.7 (2.1)	25.1 (2.5)
Minimum–maximum	22.3–24.4	19.1–28.3	24.8–28.8	23.1–28.8	19.1–28.8

as missing. Actual blood sampling times were used in all PK analyses. The maximum serum concentration (C_{max}) and time to C_{max} (T_{max}) were taken directly from the data. Subjects with measurable predose MOD-4023 serum concentrations (>5% of the corresponding C_{max}) were excluded from PK analysis. The elimination rate constant, λz, was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration–time curve. The slope was determined from a plot of the natural log of the terminal serum concentrations against time; at least 3 terminal serum concentration–time points, beginning with the final concentration ≥ LOQ, were selected for the determination of λz. The regression had to have a coefficient of determination (r^2) ≥ 0.9000, and the extrapolated portion of AUC_{inf} had to be ≤ 20%. Elimination half-life ($t_{½}$) was calculated according to the following equation.

$$t^1/_2 = \frac{0.693}{\lambda z}$$

The area under the curve (AUC) from zero to the final sample with a concentration ≥ LOQ (AUC_{0-t}) was calculated using the linear trapezoidal method and extrapolated to infinity (AUC_{inf}) using

$$AUC(\text{inf}) = AUC(0-t) + \frac{C_{tf}}{\lambda z}$$

where C_{tf} is the final concentration ≥ LOQ.

Descriptive statistics and graphic displays were used to compare the pharmacokinetics of MOD-4023 between the 2 ethnic groups.

Serum concentrations of IGF-1 and IGFBP-3 were measured by LabCorp (Burlington, North Carolina) using validated and commercially available sandwich-type chemiluminescence IGF-1 and IGFBP-3 assays (Immulite 2000, Siemens, Erlangen, Germany; IDS-iSYS, Immunodiagnostic Systems, Boldon, United Kingdom). For the IGF-1 quantitation method, samples were first acidified to dissociate IGF-1 from the binding proteins. IGF-1 and IGFBP-3 were captured by biotinylated monoclonal anti-IGF-1/anti-IGFBP-3 antibodies, which subsequently bound to streptavidin-coated magnetic particles. After incubation, acridinium-labeled anti-IGF-1 or IGFBP-3 antibodies were added to yield a directly proportional chemiluminescence signal, triggered by hydrogen

peroxide and sodium hydroxide. The range of quantitation for the assay was 10–1200 and 80–10 000 ng/mL for IGF-1 and IGFBP-3 serum concentrations, respectively. The lowest quantifiable sample concentration was 8.8 and 80 ng/mL for IGF-1 and IGFBP-3, respectively.

PD analysis was based on a noncompartmental analysis of baseline-corrected IGF-1 and IGFBP-3 concentrations. Each subject's concentrations were corrected for baseline by subtracting the predose concentration from all postdose concentrations. If the postdose concentration was less than the predose concentration, then the baseline-corrected concentration was set to 0. It should be noted that this introduces some bias, as values < 0 are set to 0, potentially overestimating concentrations. This is more likely for the vehicle group than the active groups, as the changes are much greater in the latter. The area under the effect curve ($AUEC_{0-t}$) was calculated using the linear trapezoidal method. Subjects administered vehicle were combined into a single cohort for the PD analyses. The relationship between the individual IGF-1 baseline-corrected $AUEC_{0-t}$ and MOD-4023 AUC_{0-t} was examined graphically. Based on the graphic relationship, an E_{max} model, that is,

$$E = E_0 + \frac{E\max \times C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}$$

where E represents the response, that is, baseline-corrected $AUEC_{0-t}$, E_0 is the baseline response, E_{max} is the maximum response, that is, the increase from E_0, EC_{50} is the response at 50% of E_{max}, C is the MOD-4023 AUC_{0-t}, and γ is the slope factor, was fitted to the individual subject data. All PK/PD analyses were performed using SAS v9.3 (Cary, North Carolina), SigmaPlot v12.5 (Systat Software, San Jose, California) and WinNonlin v6.2 (Pharsight, Sunnyvale, California).

Safety Evaluations

Safety was evaluated on the basis of adverse event (AE) rate and profile, physical examination, vital signs, electrocardiogram (ECG), safety laboratory assessments (hematology, biochemistry, and urinalysis), and immunogenic response (antibodies against MOD-4023, native hGH, and CTP). Adverse event were coded using the Medical Dictionary for Regulatory Activities. Tolerability was measured by local injection-site reaction assessment using the Draize score.[16] Laboratory evaluation for routine biochemistry and blood count was performed by Consolidated Medical Bioanalysis Laboratory (Cypress, California). Blood samples (8.5 mL per sample) for binding and neutralizing antibodies against MOD-4023, native hGH, and CTP were collected predose and 7 and 30 days (±2 days) postinjection. All samples were stored at -20°C until analysis. Each sample was analyzed in screening format. Samples reactive for anti-MOD-4023 antibodies were confirmed for MOD-4023 in an immunocompetition assay (bridge enzyme-linked immunosorbent assay, sensitivity < 100 ng/mL). Samples confirmed as positive for anti-MOD-4023 binding antibodies were titered and further characterized for anti-CTP and anti-GH specificity, as well as for neutralizing activity against MOD-4023 and hGH (cell-based assay). All immunogenicity assays were performed by Intertek Pharmaceutical Services.

Results

Subject Disposition and Characteristics

A total of 42 subjects, randomized by dose and ethnic group, were enrolled in and completed the study (Table 1). Five subjects had a serum MOD-4023 concentration prior to dosing that was ≥ LOQ (150 pg/mL). Of those, 2 subjects in the 2.5-mg cohort (1 Caucasian and 1 Japanese) had measurable predose MOD-4023 serum concentrations (>5% of the corresponding C_{max}) and therefore were not used for PK evaluation purposes. The data for those subjects for MOD-4023 was excluded from the descriptive statistics for serum concentrations and PK parameters. To maintain balance between the PK and PD analyses, these subjects were also excluded from the descriptive statistics for the PD analyses and from the PK/PD analysis. Therefore, the analysis population consisted of 40 subjects, 3 of each ethnic group receiving vehicle, 5 Caucasian and 5 Japanese subjects receiving 2.5 mg, and 6 of each ethnic group receiving 7.5 and 15 mg of MOD-4023.

Pharmacokinetics

The arithmetic mean MOD-4023 serum concentrations for Japanese and Caucasian subjects are shown in Figure 2. There does not appear to be a difference between Japanese and Caucasian subjects with respect to PK parameters for the 2.5- and 7.5-mg dose groups. The arithmetic mean $t_{½}$ was independent of dose and ethnic group, ranging from 18.2 to 24.5 hours. For the 15-mg dose group, the mean C_{max} was lower, and the median T_{max} was longer in Japanese compared with Caucasian subjects, although the mean values for AUC_{inf} were comparable (Table 2). The individual subject values for AUC_{inf} were compared between Japanese and Caucasian subjects by dose. Within each cohort there was a complete overlap between the 2 ethnic groups. For both Caucasian and Japanese subjects, there was a greater than proportional increase in AUC_{inf} with dose. Although the log–log plots of the individual subject AUC_{inf} versus dose were linear, the slope for both ethnic groups was >1, indicating a

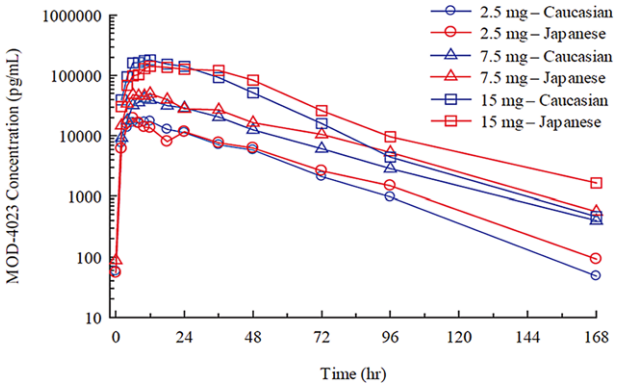

Figure 2. Serum concentration–time profile of MOD-4023 in healthy Caucasian and Japanese subjects. Arithmetic mean serum concentrations of MOD-4023 after subcutaneous injection of a single 2.5-, 7.5-, or 15-mg dose of MOD-4023 to healthy Caucasian and Japanese subjects are plotted against time using a semilogarithmic axis.

greater than proportional increase. The slope was the same (1.41) for both groups (results not shown).

Pharmacodynamics

There were no apparent differences in the arithmetic mean plasma concentrations of IGF-1 between Japanese and Caucasian subjects for the vehicle and 2.5- and 7.5-mg dose groups, although those for the Japanese subjects were lower than for the Caucasian subjects after a dose of 15 mg. Within each dosing cohort, the arithmetic mean values for baseline-corrected C_{max} and AUEC were comparable (Figure 3A and Table 3). Mean plasma concentrations of IGFBP-3, either uncorrected or corrected for baseline, were variable but did not appear to differ between Japanese and Caucasian subjects for the vehicle and 2.5-, 7.5-, and 15-mg dose groups. Similarly, within each dosing group, mean values for baseline-corrected C_{max} and AUEC were comparable when the variability was taken into consideration (Figure 3B and Table 3). The relationship between the individual subject IGF-1 $AUEC_{0-t}$ and MOD-4023 AUC_{0-t} showed a classic E_{max} pattern (Figure 4). There was no apparent difference in the relationship as a function of dose or ethnicity, and a single E_{max} function was consistent with the observed data. The model-predicted IGF-1 $AUEC_{0-t}$ was consistent with the observed data, with no apparent differences between Caucasian and Japanese subjects. The estimated model parameters were an E_{max} of 45 021 ± 9683 ng·h/mL with an EC_{50} of 1 529 064 ± 619 471 pg·h/mL and E_0 of 1894 ± 3577 ng·h/mL.

Safety

Nine subjects (9 of 42; 21.4%) reported 9 treatment-related adverse events (AEs), 1 each over the course of the study (3 subjects in the Japanese and 6 in the Caucasian ethnic groups; see Table 4). All but 1 of

Table 2. Summary of Pharmacokinetic Parameters for MOD-4023 After Subcutaneous Injection of a Single Dose of MOD-4023 in Healthy Caucasian and Japanese Subjects

	MOD-4023 Dose		
Parameter[a]	2.5 mg (n = 12)	7.5 mg (n = 12)	15 mg (n = 12)
Caucasian			
C_{max} (pg/mL)	19 549 ± 11 972 (5)	48 434 ± 33 634 (6)	191 629 ± 57 450 (6)
T_{max} (h)	10 (5)	15 (6)	10 (6)
	[4–24]	[6–24]	[6–12]
AUC_{0-t} (pg·h/mL)	664 285 ± 372 730 (5)	1 659 296 ± 666 246 (6)	6 898 680 ± 1 979 167 (6)
AUC_{inf} (pg·h/mL)	568 529 ± 350 275 (3)	1 674 510 ± 660 225 (6)	6 544 415 ± 1 973 482 (5)
$t_{½}$ (h)	20.7 ± 1.2 (3)	24.9 ± 4.8 (6)	18.2 ± 1.3 (5)
CL/F (L/h)	5.48 ± 2.71 (3)	5.31 ± 2.83 (6)	2.52 ± 0.97 (5)
Vz/F (L)	167 ± 90 (3)	205 ± 160 (6)	66.9 ± 28.2 (5)
Japanese			
C_{max} (pg/mL)	21 007 ± 14 189 (5)	53 888 ± 21 933 (6)	160 119 ± 133 842 (6)
T_{max} (hr)	6 (5)	12 (6)	15 (6)
	[4–24]	[6–18]	[10–48]
AUC_{0-t} (pg·h/mL)	666 653 ± 292 498 (5)	2 249 654 ± 661 585 (6)	7 502 269 ± 5 170 529 (6)
AUC_{inf} (pg·h/mL)	517 191 ± 218 017 (3)	2 259 967 ± 742 595 (5)	7 561 858 ± 5 141 184 (6)
$t_{½}$ (h)	22.1 ± 8.2 (3)	22.4 ± 2.0 (5)	21.9 ± 7.2 (6)
CL/F (L/h)	5.44 ± 2.23 (3)	3.61 ± 1.15 (5)	3.24 ± 2.73 (6)
Vz/F (L)	191 ± 135 (3)	118 ± 40 (5)	122 ± 132 (6)

AUC, area under curve; CL/F, apparent total clearance; C_{max}, maximal concentration; $t_{½}$, half-life; T_{max}, time of maximal concentration; Vz/F, apparent volume of distribution.

[a]Arithmetic mean ± standard error (n) except T_{max}, for which the median (n) [range] is reported.

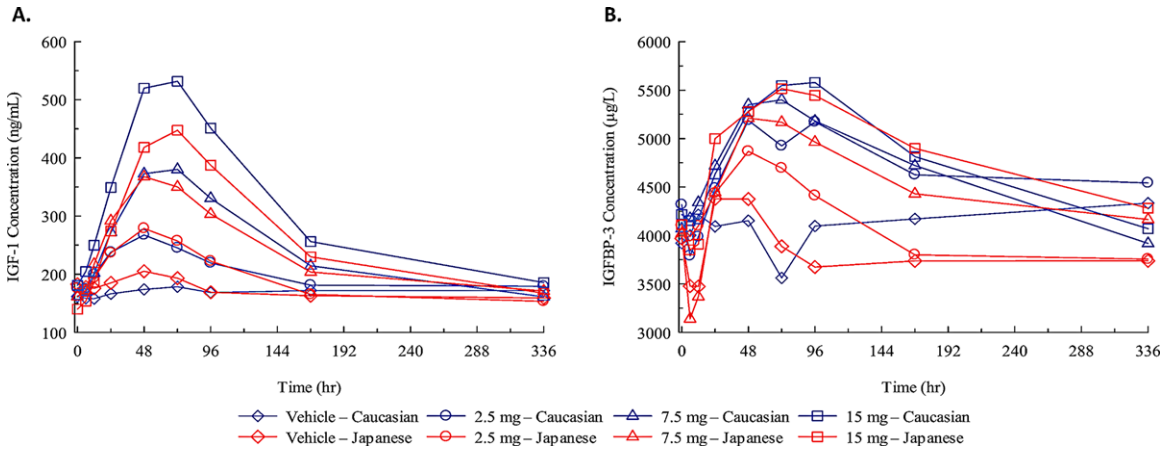

Figure 3. IGF-1 and IGFBP-3 plasma concentrations following MOD-4023 or placebo (vehicle) administration in healthy Caucasian and Japanese subjects. Arithmetic mean plasma concentrations over time (uncorrected for baseline) of IGF-1 and IGFBP-3 after subcutaneous injection of a single 2.5-, 7.5-, or 15-mg dose are shown in A and B, respectively.

Table 3. Summary of PD Parameters (Baseline-Corrected) After Subcutanoeus Injection of a Single Dose of MOD-4023 or Placebo in Healthy Caucasian and Japanese Subjects

		MOD-4023 Dose		
Parameter[a]	Placebo (n = 6)	2.5 mg (n = 12)	7.5 mg (n = 12)	15 mg (n = 12)
IGF-1				
Caucasian				
C_{max} (ng/mL)	22.0 ± 2.6 (3)	91.0 ± 15.8 (5)	227 ± 55.8 (6)	361 ± 28.4 (6)
T_{max} (h)	72.1 (3) [48.0–168]	48.0 (5) [48.0–48.0]	72.0 (6) [48.0–72.5]	72.0 (6) [48.0–72.0]
AUEC (ng·h/mL)	3726 ± 1767 (3)	8609 ± 2593 (5)	27 745 ± 7256 (6)	43 694 ± 6883 (6)
Japanese				
C_{max} (ng/mL)	22.3 ± 12.9 (3)	103 ± 31.5 (5)	210 ± 39.5 (6)	315 ± 74.3 (6)
T_{max} (h)	48.0 (3) [48.0–48.0]	48.0 (5) [48.0–48.0]	48.0 (6) [48.0–72.0]	72.0 (6) [48.0–96.1]
AUEC (ng·h/mL)	945 ± 801 (3)	10 652 ± 4606 (5)	25 580 ± 7803 (6)	41 437 ± 7170 (6)
IGFBP-3				
Caucasian				
C_{max} (ng/mL)	582 ± 73.4 (3)	1241 ± 742 (5)	1398 ± 608 (6)	1474 ± 560 (6)
T_{max} (h)	336 (3) [12.0–336]	48.0 (5) [48.0–168]	60.0 (6) [48.0–72.5]	84.0 (6) [48.0–96.0]
AUEC (ng·h/mL)	91 869 ± 22 013 (3)	189 323 ± 182 272 (5)	218 493 ± 98 823 (6)	218 616 ± 116 326 (6)
Japanese				
C_{max} (ng/mL)	495 ± 211 (3)	832 ± 382 (5)	1312 ± 387 (6)	1568 ± 309 (6)
T_{max} (h)	48.0 (3) [24.0–48.0]	48.0 (5) [48.0–96.0]	48.0 (6) [48.0–97.2]	84.0 (6) [72.0–168]
AUEC (ng·h/mL)	20 289 ± 9344 (3)	66 757 ± 30 069 (5)	187 185 ± 100 203 (6)	267 594 ± 118 384 (6)

[a] Arithmetic mean ± standard error (n) except T_{max}, for which the median (n) [Range] is reported.

these AEs were mild in intensity (8 of 9; 88.9%); 1 Caucasian subject in the 15 mg MOD-4023 group experienced moderate-intensity otitis media. None of the AEs were considered severe or serious, and none led to early discontinuation. Overall, the proportion of subjects with treatment-related AEs was similar between the vehicle and the lower doses of MOD-4023 (1 to 2 subjects in each treatment group; none to 1 in each ethnic group); 5 subjects in the 15-mg MOD-4023 dose group reported treatment-related AEs (1 Japanese subject and 4 Caucasian subjects). The most commonly reported AE that was considered treatment related was upper respiratory tract infection, reported by 4 subjects, 2 in each ethnic group. There were no treatment-related

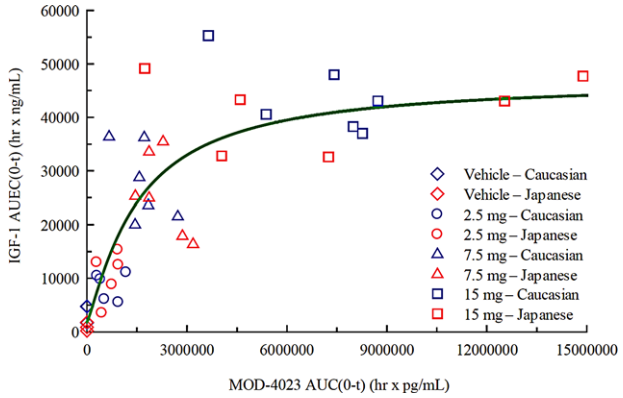

Figure 4. PK/PD analysis of MOD-4023. The relationship between the individual subject baseline-corrected IGF-1 $AUEC_{0-t}$ and MOD-4023 AUC_{0-t} after subcutaneous injection of a single 0- (vehicle), 2.5-, 7.5-, or 15-mg dose of MOD-4023 to healthy Caucasian and Japanese subjects. Model parameters (estimate ± standard error): E_0 = 1894 ± 3577 ng·h/mL; E_{max} = 45 021 ± 9683 ng·h/mL; EC_{50} = 1 529 064 ± 619 471 pg·h/mL; γ = 1.19 ± 0.49; correlation coefficient (r) = 0.8446 with 37 *df* ($P < .05$).

AEs associated with local tolerability issues. Following subcutaneous administration of MOD-4023, 16 subjects experienced erythema (10 Caucasian, 6 Japanese), and 2 subjects experienced very slight edema (1 Caucasian subject in the 7.5-mg MOD-4023 dose group and 1 Japanese subject in the 2.5-mg MOD-4023 dose group); none of these events were associated with the injection site. Of the 16 subjects with erythema, 1 was in the vehicle group, 6 in the 2.5-mg MOD-4023 dose group (5 Caucasian, 1 Japanese), 4 in the 7.5-mg MOD-4023 dose group (2 Caucasian, 2 Japanese), and 5 in the 15-mg MOD-4023 dose group (2 Caucasian, 3 Japanese). All cases of erythema but one were reported as very slight (barely perceptible). One Japanese subject (2.5-mg MOD-4023 dose group) reported a well-defined erythema 12 hours postdose. All cases but one were observed on dosing day between 30 minutes and 24 hours postdose, with the majority of cases occurring within 4 hours postdose; 1 Caucasian subject had very slight erythema 168 hours postdose.

In all MOD-4023 doses and ethnic groups, no clinically relevant immunogenic response was observed. All but one subject had negative results on an anti-MOD-4023-binding specificity test. At the end of the study, 1 Japanese subject from the 15-mg dose group had a positive result (below 10) for the MOD-4023-binding specificity and negative results for the neutralizing antibodies for MOD-4023 and native hGH. There were no apparent differences across dose groups among other safety parameters, including laboratory evaluation, vital signs, and ECGs; few postdose abnormalities were observed in either ethnic group and with no consistent pattern.

Discussion

MOD-4023, a long-acting CTP-modified hGH, was developed as a once-weekly subcutaneous injection in children and adults, using OPKO's CTP technology to significantly prolong the protein's half-life. This phase 1 study compared the safety, tolerability, clinical pharmacology (PK and PD), and safety of MOD-4023 in healthy adult male Caucasian subjects with Japanese subjects. The PK parameters observed in this study were consistent with those reported previously for MOD-4023.[8,9] There were essentially no differences in mean MOD-4023 serum concentrations between Japanese and Caucasian subjects in the 2.5- and

Table 4. Incidence of Treatment-Related AEs by Dose and Ethnic Group

		MOD-4023			
	Placebo (n = 6)	2.5 mg (n = 12)	7.5 mg (n = 12)	15 mg (n = 12)	Total (n = 42)
Japanese subjects					
Number of subjects with at least 1 treatment-related AE	1	0	1	1	3
Upper respiratory tract infection	1	0	0	1	2
Back pain	0	0	1	0	1
Caucasian subjects					
Number of subjects with at least 1 treatment-related AE	1	1	0	4	6
Sensation of foreign body	1	0	0	0	1
Otitis media	0	0	0	1	1
Upper respiratory tract infection	0	1	0	1	2
Headache	0	0	0	1	1
Nasal congestion	0	0	0	1	1

7.5-mg cohorts. In the 15-mg group, MOD-4023 concentrations in Japanese subjects were lower during the initial 24 hours compared with Caucasian ubjects (and vice versa from 24 hours onward), suggesting a slower rate of absorption. When the small number of subjects and associated variability are taken into account, there does not appear to be a difference between Japanese and Caucasian subjects with respect to PK parameters for the 2.5- and 7.5-mg cohorts. For the 15-mg cohort, the lower mean C_{max} and longer median T_{max} in Japanese subjects compared with Caucasian subjects, combined with a comparable mean AUC_{inf}, also suggest slower absorption. The similar proportional increase in AUC_{inf} with dose further supports the comparability of the PK parameters of MOD-4023 between Japanese and Caucasian subjects. With respect to the PD of MOD-4023 after single subcutaneous doses of 2.5, 7.5, and 15 mg, as measured by IGF-1 and IGFBP-3 plasma concentrations, no apparent differences were observed between Japanese and Caucasian subjects. The apparent E_{max} relationship between the PD effect of MOD-4023, as measured by IGF-1 $AUEC_{0-t}$ for baseline-corrected concentrations and MOD-4023 AUC_{0-t} was not dependent on dose or ethnicity and indicates that a dose of 15 mg achieves the maximal effect in Japanese and Caucasian subjects.

MOD-4023 demonstrated a favorable safety profile and local tolerance following subcutanoeus administration of a single dose. There was no consistent pattern of any abnormalities in safety parameters attributable to the study intervention across MOD-4023 dose groups, particularly in the lower doses (2.5 and 7.5 mg). Taken together, the current study demonstrates no discernible differences in the PK, PD, and safety profile of MOD-4023 between Japanese and Caucasian subjects and provides additional support for the potential of MOD-4023 as a long-acting hGH formulation, to be further developed for a regimen of once-weekly administration.

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Declaration of Conflicting Interests

W.G.K is a consultant for OPKO Biologics. M.J.M., R.K., O.H., and G.H. have nothing to disclose.

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