

## **Clinical Pharmacodynamic Effects of the Growth Hormone Receptor Antagonist Pegvisomant: Implications for Cancer Therapy**

Donghua Yin, Franzanne Vreeland, Larry J. Schaaf, Robert Millham, Barbara A. Duncan, and Amarnath Sharma

**Abstract Purpose:** The present study evaluated and compared the efficacy of pegvisomant and octreotide in blocking the growth hormone (GH) axis in humans based on pharmacodynamic biomarkers associated with the GH axis. The study also evaluated the safety of pegvisomant given at high s.c. doses for 14 days.

**Experimental Design:** Eighty healthy subjects were enrolled in five cohorts: cohorts 1 to 3, s.c. pegvisomant at 40, 60, or 80 mg once daily  $\times$  14 days ( $n = 18$  per cohort); cohort 4, s.c. octreotide at 200  $\mu$ g thrice daily  $\times$  14 days ( $n = 18$ ); and cohort 5, untreated control ( $n = 8$ ). Serial blood samples were collected to measure plasma concentrations of total insulin-like growth factor type I (IGF-I), free IGF-I, IGF-II, IGF-binding protein 3 (IGFBP-3), and GH in all subjects and serum pegvisomant concentrations in subjects of cohorts 1 to 3. All subjects receiving treatment were monitored for adverse events (AE).

**Results:** After s.c. dosing of pegvisomant once daily for 14 days, the mean maximum suppression values of total IGF-I were 57%, 60%, and 62%, at 40, 60, and 80 mg dose levels, respectively. The maximum suppression was achieved  $\sim$  7 days after the last dose and was sustained for  $\sim$  21 days. Pegvisomant also led to a sustained reduction in free IGF-I, IGFBP-3, and IGF-II concentrations by up to 33%, 46%, and 35%, respectively, and an increase in GH levels. In comparison, octreotide resulted in a considerably weaker inhibition of total IGF-I and IGFBP-3 for a much shorter duration, and no inhibition of IGF-II. AEs in pegvisomant-treated subjects were generally either grade 1 or 2. The most frequent treatment-related AEs included injection site reactions, headache, and fatigue.

**Conclusions:** Pegvisomant at well-tolerated s.c. doses was considerably more efficacious than octreotide in suppressing the GH axis, resulting in substantial and sustained inhibition of circulating IGF-I, IGF-II, and IGFBP-3 concentrations. These results provide evidence in favor of further testing the hypothesis that pegvisomant, through blocking the GH receptor – mediated signal transduction pathways, could be effective in treating tumors that may be GH, IGF-I, and/or IGF-II dependent, such as breast and colorectal cancer.

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Pegvisomant is a modified human growth hormone (GH) conjugated with polyethylene glycol (PEG) moieties (1, 2). Clinically, pegvisomant has been indicated for treatment of acromegaly, a chronic endocrine disease usually caused by a GH-hypersecretive pituitary adenoma (3–6). The elevated level of GH in patients with acromegaly leads to excessive GH receptor (GHR) activation and overproduction of insulin-like growth factor type I (IGF-I), causing a series of debilitating signs and symptoms, such as coarse facial features, acral enlargement, headaches, arthropathy, hypertension, and glucose intolerance (7). Pegvisomant competes with endogenous GH for binding to the GHR but does not activate the receptor, thereby blocking the GH-initiated signaling and IGF-I production (2). The significantly elevated circulating IGF-I concentrations in acromegalic patients can be suppressed to the reference range after treatment with daily s.c. pegvisomant at doses of 10 to 30 mg

(4, 6). In fact, pegvisomant is regarded as the most effective treatment for normalizing IGF-I in acromegaly (8).

Cumulating evidence indicates that excessive GH/GHR signaling, through mechanisms dependent or independent of the IGF-I/IGF-I receptor system, is associated with the development and progression of several common cancers, including colorectal, prostate, and breast cancer. It has been reported that patients with acromegaly have a higher incidence of colorectal cancer (9–11). Elevated GHR expression has been observed in colorectal, prostate, and breast cancer tissues (12–15), and this overexpression is correlated with poor response of rectal cancer to radiotherapy (16). It has also been shown that autocrine production of GH exerts direct proliferative and antiapoptotic effects on human mammary carcinoma cells and converts these cells to an invasive phenotype (17, 18). At the molecular level, GH-induced activation of GHR initiates multiple signaling pathways, including Janus-activated kinase 2/signal transducers and activators of transcription, Ras/Raf/mitogen-activated protein kinase, and insulin receptor substrate-1/phosphatidylinositol-3-kinase/Akt (19–21). Activation of the mitogen-activated protein kinase and phosphatidylinositol-3-kinase/Akt signaling cascades have been shown to be involved in promoting cell transformation and tumor cell proliferation, differentiation, survival, and metastasis (22–25). Furthermore, multiple classes of pharmacologic agents that inhibit GH/GHR signaling at different levels have shown anticancer activity in both *in vitro* and *in vivo* tumor models; these agents include GH-releasing hormone antagonists, somatostatin analogues, GH receptor antagonist, and IGF-I receptor targeting antibodies or small-molecule inhibitors (26–32). Together, all these evidences point to blockade of GH axis as an attractive strategy for cancer therapy.

Of the limited number of reported clinical studies evaluating the anticancer activity from GH signaling blockade, the vast majority were conducted with two of the somatostatin analogues, octreotide and lanreotide (33, 34). These clinical trials evaluated the safety and anticancer effectiveness of octreotide or lanreotide as a single agent or in combination with approved therapy in a number of tumor types, including breast, prostate, lung, colorectal, gastric, and pancreatic cancer. Nevertheless, the anticancer activity observed for these agents has not been sufficient to justify the approval of these somatostatin analogues for routine use in cancer patients, except in those with certain neuroendocrine tumors (33). One of the likely reasons for the largely unimpressive anticancer activity with the somatostatin analogues has been attributed to their apparently limited ability in suppressing GH signaling, resulting in reduction of circulating IGF-I concentrations by no more than 50% (34).

Despite the well-established effectiveness of pegvisomant in antagonizing excessive GH/GHR signaling in patients with acromegaly, the anticancer activity of pegvisomant has not been evaluated clinically. In *in vitro* and human tumor xenograft studies, pegvisomant as a single agent or in combination with cytotoxic chemotherapeutic agents showed anticancer activities against a range of tumor models, including those of colon and breast carcinoma and meningioma (30, 32, 35, 36). Before further evaluation of the antitumor efficacy of pegvisomant in cancer patients, it is important to identify a safe dose and dosing regimen of pegvisomant that can suppress the GH axis more effectively than existing somatostatin analogues. Thus, the

present study was conducted to assess and compare the clinical efficacy of pegvisomant and octreotide in suppressing GH/GHR signaling with the use of GH axis-related biomarkers. The pharmacokinetics and pharmacodynamics of pegvisomant were evaluated to guide the selection of dose and dosing regimen for further evaluation in cancer patients.

## Materials and Methods

**Study design and drug formulation.** This was a phase 1, open-label, dose-escalation trial conducted in 80 healthy adult male and female subjects. Fifty-four subjects grouped in three cohorts (18 per cohort) received pegvisomant s.c. at once daily (QD) doses of 40, 60, and 80 mg for 14 days. Another cohort of 18 subjects received octreotide s.c. at 200 µg thrice daily (TID) for 14 days. Eight additional subjects were enrolled as untreated controls to evaluate the normal variability in total IGF-I and other biomarkers over a 9-week period. The sample size of each treatment cohort was estimated for the study to have at least 80% power to detect a 50% difference in the mean IGF-I suppression between pegvisomant and octreotide. All dose administrations were done at the Clinic Unit of the Jasper Clinical Research and Development, Inc. (Kalamazoo, MI), by designated clinical staff, under the supervision of the investigator or the investigator's deputy on site.

Octreotide was used as a control for the activity of GH axis suppression. When used for treatment of acromegaly, octreotide is found to be effective in most patients at 100 µg TID, with doses higher than 300 µg/d seldom providing additional biochemical benefit (37). Octreotide at 200 µg TID has been used in a number of trials in cancer patients for evaluation of the single-agent anticancer activity (33, 34). Based on this information, the octreotide dose of 200 µg TID was selected for use in the present trial.

Pegvisomant was supplied as sterile, lyophilized white powder in glass vials containing 10, 15, or 20 mg/vial of the active drug substance and the excipients mannitol, glycine, and sodium phosphate. Octreotide acetate (Sandostatin) was supplied as a clear sterile solution containing 200 or 1,000 µg/mL of octreotide acetate salt and lactic acid, mannitol, sodium bicarbonate, and water.

The study was approved by the Institutional Review Board/Independent Ethics Committee and was conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines, the ethical principles originating in or derived from the Declaration of Helsinki, and the Food and Drug Administration Regulations (Title 21 Code of Federal Regulations, parts 50, 56, and 312). Study subjects were financially compensated. Written informed consent was obtained from each subject before study entry.

**Pharmacokinetic and biomarker sampling.** In subjects given pegvisomant (cohorts 1-3), blood samples for measurement of serum pegvisomant concentrations were collected before dosing on days 1 (time 0), 4, 8, 10, 12, 13, and 14. For subjects in the 60 and 80 mg cohorts, additional blood samples for measuring pegvisomant concentrations were collected every 7 days for up to day 70 after the last pegvisomant dose.

In pegvisomant- or octreotide-treated subjects, serial blood samples were collected to measure plasma concentrations of total IGF-I, free IGF-I, IGF-II, IGF binding protein-3 (IGFBP-3), and GH on day -1 (~24 h before the first dose); predose on day 1 (time 0); and on days 2, 3, 4, 5, 6, 8, 10, 12, 13, and 14. For pegvisomant-treated subjects, additional samples for total IGF-I measurement were collected every 7 days for up to day 77, and an additional sample for measuring the other biomarkers was collected on day 28 (14 days after the last dose). For octreotide-treated subjects, an additional sample was collected on day 21 (7 days after the last dose) for measuring all the biomarkers.

For subjects enrolled as untreated controls, blood samples for measurement of plasma concentrations of total IGF-I, free IGF-I, IGF-II, IGFBP-3, and GH were collected weekly for 63 days (9 weeks).

**Measurement of pegvisomant and biomarker concentrations.** Validated analytic methods were used to assay serum concentrations of pegvisomant and plasma concentrations of total IGF-I, free IGF-I, IGF-II, IGFBP-3, and GH.

Serum pegvisomant concentrations were determined by RIA based on the principle of a competitive protein binding technique. In essence, the concentration of pegvisomant was quantitated by its competition with a trace amount of radiolabeled antigen ( $[^{125}\text{I}]\text{B2036}$ ) for rabbit anti-B2036 antibody binding sites. Radioactive  $[^{125}\text{I}]\text{B2036}$  and nonradioactive pegvisomant (present in the unknown, standard, or control human serum samples) were incubated under suitable assay conditions. Separation of the free  $[^{125}\text{I}]\text{B2036}$  from the antibody-bound fraction is accomplished by second antibody precipitation method. The antibody-bound fraction was precipitated and counted in a gamma counter. The concentrations of pegvisomant in the unknown clinical samples were quantitated by comparison with the dose-response curve. The lower limit of quantification (LLOQ) for the assay was 0.100  $\mu\text{g}/\text{mL}$ ; the interassay precision [overall percentage coefficient of variation (CV%)] and the bias were <18% and 6%, respectively, in the calibration range of 0.100 to 2.20  $\mu\text{g}/\text{mL}$ .

Plasma concentrations of total IGF-I were determined using a quantitative sandwich enzyme immunoassay technique. Standards and quality control samples were prepared using recombinant human IGF-I purchased from the National Institute for Biological Standards and Control. Antibodies to IGF-I were purchased from R&D Systems (Minneapolis, MN) as part of an ELISA kit designed to measure human IGF-I (R&D Systems Quantikine Human IGF-I Immunoassay). EDTA human plasma samples and quality controls were pretreated with an acid/ethanol solution to release IGF-I from binding proteins to quantitate the total amount of IGF-I. Standards, pretreated samples, and quality controls were added to a plate coated with a monoclonal antibody specific for IGF-I. Any IGF-I present was bound by the immobilized antibody. After washing away any unbound substances, a polyclonal antibody specific for IGF-I conjugated to horseradish peroxidase was added to the plate. Following an incubation period, the plate was washed to remove any unbound horseradish peroxidase conjugate. A tetramethylbenzidine substrate solution was added, and color developed in proportion to the amount of IGF-I bound in the initial step. The color development was stopped, and the intensity of the color was measured. The concentrations of IGF-I in the unknown clinical samples were quantitated by comparison with the dose-response curve. The LLOQ for the assay was 9.94  $\text{ng}/\text{mL}$ ; the interassay precision (overall CV%) and the bias were <23% and 13%, respectively, in the calibration range of 9.94 to 399  $\text{ng}/\text{mL}$ .

Plasma concentrations of free IGF-I were determined by using a quantitative sandwich enzyme immunoassay technique. Standards and quality control samples were prepared using recombinant human IGF-I purchased from the National Institute for Biological Standards and Control. Antibodies to IGF-I were purchased from R&D Systems. Standards, quality controls, and study samples were added to a microtiter plate coated with monoclonal anti-IGF-I antibody. After appropriate incubation and a washing step, polyclonal anti-IGF-I detection antibody labeled with biotin was added to all wells. After a second incubation and washing step, a streptavidin-horseradish peroxidase conjugate was added to all wells. After a third incubation and washing step, the substrate solution (tetramethylbenzidine) was added, and color developed in proportion to the amount of free IGF-I bound in the initial step. The color development was stopped by the addition of an acidic solution, and the intensity of color was measured. The concentrations of free IGF-I in the unknown clinical samples were quantitated by comparison with the dose-response curve. The LLOQ for the assay was 0.050  $\text{ng}/\text{mL}$ ; the interassay precision (overall CV%) and the bias were <8% and 1%, respectively, in the calibration range of 0.050 to 2.10  $\text{ng}/\text{mL}$ .

Plasma concentrations of IGF-II were determined using a quantitative sandwich enzyme immunoassay technique. Standards and quality control samples were prepared using recombinant human IGF-II

purchased from the National Institute for Biological Standards and Control. Antibodies to IGF-II were purchased from R&D Systems. Before assay, standards, quality controls, and study samples were pretreated using an acid/ethanol extraction procedure to dissociate and separate IGF-II from its binding proteins. After extraction, pretreated samples were added to a microtiter plate coated with monoclonal anti-IGF-II antibody. After appropriate incubation and a washing step, polyclonal anti IGF-II detection antibody, labeled with biotin, was added to all wells. After a second incubation and washing step, a streptavidin horseradish peroxidase conjugate is added to all wells. After a third incubation and washing step, the substrate solution (tetramethylbenzidine) was added, and color developed in proportion to the amount of IGF-II bound in the initial step. The color development was stopped by the addition of an acidic solution, and the intensity of color was measured. The concentrations of IGF-II in the unknown clinical samples were quantitated by comparison with the dose-response curve. The LLOQ for the assay was 50.0  $\text{ng}/\text{mL}$ ; the interassay precision (overall CV%) and the bias were <10% and 7%, respectively, in the calibration range of 50.0 to 1,000  $\text{ng}/\text{mL}$ .

Plasma concentrations of IGFBP-3 were determined using a quantitative sandwich enzyme immunoassay technique. The recombinant human IGFBP-3 used in preparation of standards and quality control samples, as well as antibodies to IGFBP-3, were purchased from R&D Systems. Standards, quality controls, and study samples were added to a microplate precoated with a monoclonal antibody specific for IGFBP-3. The immobilized antibody bound any IGFBP-3 present. After an incubation period, the plate was washed to remove any unbound substances. An enzyme-linked polyclonal antibody specific for IGFBP-3 was added to the microplate. Following another incubation period, the plate was washed again to remove any unbound antibody-enzyme reagent. A substrate solution was added, and color developed in proportion to the amount of IGFBP-3 bound in the initial step. The color development was stopped, and the intensity of the color was measured. The concentrations of IGFBP-3 in the unknown clinical samples were quantitated by comparison with the dose-response curve. The LLOQ for the assay was 0.700  $\text{ng}/\text{mL}$ ; the interassay precision (overall CV%) and the bias were <10% and 2%, respectively, in the calibration range of 0.700 to 50.0  $\text{ng}/\text{mL}$ .

Plasma concentrations of human GH were determined using a quantitative specific sandwich enzyme immunoassay technique designed to be free of interference from pegvisomant. From a panel of monoclonal antibodies raised against human GH, a pair of antibodies were identified by Neuroendocrine Unit Laboratories, Medizinische Klinik Innenstadt der Ludwig-Maximilians University (Munich, Germany) for targeting epitopes in receptor binding sites 1 and 2, respectively, which have mutated in the human GH analogue. Neither of the monoclonal antibodies selected showed cross-reaction with pegvisomant. Combining these antibodies (names 8B11 and 6C1) in a sandwich assay led to a linear dose relationship. Standards were prepared from human GH purchased from the National Institute for Biological Standards and Control. Quality control specimens were prepared by pooling human sera from donors with high and low levels of human GH. Additional controls were prepared using pooled sera added to pegvisomant. The concentrations of GH in the unknown clinical samples were quantitated by comparison with the dose-response curve. The LLOQ for the assay was 0.200  $\text{ng}/\text{mL}$ ; the interassay precision (overall CV%) and the bias were <18% and 5%, respectively, in the calibration range of 0.200 to 50.0  $\text{ng}/\text{mL}$ .

**Safety monitoring.** Subjects were monitored for the type and severity (mild, moderate, severe, and life threatening) of any adverse events (AE) during the study and follow-up period. Clinical laboratory tests for hematology, chemistry, and urinalysis were done during the study period. Before dosing or after drug administration, subjects were also monitored for vital signs, including pulse, blood pressure, respiration, and temperature. Additionally, a single 12-lead electrocardiogram was obtained on all subjects at screening.

**Table 1.** Demographics and baseline characteristics of enrolled subjects

	Cohort				
	Pegvisomant (mg/d)			Octreotide ( $\mu\text{g TID}$ )	Untreated
	40	60	80	200	
<i>n</i>	18	18	18	18	8
Male	9	13	7	13	5
Female	9	5	11	5	3
Age (y)	29.6 $\pm$ 8.8 (19.0-47.0)	26.7 $\pm$ 10.0 (18.0-49.0)	28.2 $\pm$ 9.2 (19.0-46.0)	30.5 $\pm$ 10.1 (18.0-52.0)	31.9 $\pm$ 9.2 (19.0-46.0)
Weight (kg)	72.7 $\pm$ 10.7 (51.3-90.7)	75.9 $\pm$ 12.0 (54.9-94.3)	72.2 $\pm$ 10.8 (56.2-90.7)	75.6 $\pm$ 11.5 (50.8-94.8)	72.1 $\pm$ 7.6 (63.5-84.8)
Body mass index (kg/m <sup>2</sup> )	24.4 $\pm$ 2.4 (19.4-30.0)	25.4 $\pm$ 2.9 (20.7-30.0)	24.7 $\pm$ 2.3 (21.4-28.3)	25.5 $\pm$ 2.9 (19.5-29.8)	24.2 $\pm$ 2.7 (20.7-28.0)
Height (cm)	172.6 $\pm$ 10.4 (154.9-186.7)	172.7 $\pm$ 9.7 (154.9-185.4)	170.5 $\pm$ 9.5 (157.5-188.0)	172.1 $\pm$ 8.4 (153.7-190.5)	172.7 $\pm$ 7.3 (162.6-182.9)

AEs were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). AEs included adverse drug reactions, illnesses with onset during the study, exacerbation of previous illnesses, and any clinically significant changes in physical examination findings and abnormal objective test findings (e.g., vital signs or laboratory). If the AE or its sequelae persisted, follow-up monitoring continued until resolution or stabilization. Causality assessment was done for all AEs. Any AEs with unknown causality were attributed to the study drug.

**Pharmacokinetic and biomarker data analysis.** Serum pegvisomant concentration-time data were analyzed by noncompartmental methods using WinNonlin v.3.2 (Pharsight, Mountain View, CA). Serum predose trough concentration on day 14 ( $C_{\text{trough, day14}}$ ) was determined from individual subject data. Area under the trough serum concentration-time curve (AUC) from time 0 to day 14 ( $\text{AUC}_{0\text{-day14}}$ ) was determined using the linear/logarithmic trapezoidal approximation. The terminal elimination rate constant ( $\lambda_z$ ) was determined by linear least-squares regression of the terminal log-linear phase after logarithmic transformation of individual concentration-time data. The apparent elimination half-life ( $t_{1/2}$ ) was calculated as  $\ln 2/\lambda_z$ . Area under the concentration-time curve from time 0 to the last time at which quantifiable concentrations occurred ( $\text{AUC}_{0\text{-Tlast}}$ ) was also obtained by linear/logarithmic trapezoidal approximation. Area under the concentration-time curve from the time  $T_{\text{last}}$  to infinity ( $\text{AUC}_{\text{Tlast-inf}}$ ) was calculated as  $C_{\text{Tlast}}/\lambda_z$ , where  $C_{\text{Tlast}}$  is the estimated concentration at time  $T_{\text{last}}$  based on aforementioned regression analysis. Area under the plasma concentration-time curve from time 0 to infinity ( $\text{AUC}_{0\text{-inf}}$ ) was estimated as the sum of  $\text{AUC}_{0\text{-Tlast}}$  and  $\text{AUC}_{\text{Tlast-inf}}$ .

Of the 80 subjects enrolled in the study, four subjects (three in pegvisomant cohorts and one in the octreotide cohort) were not included in the pharmacokinetic and biomarker data analyses because of incomplete dosing and inadequate sampling. Two pegvisomant-treated subjects (one each in 40 and 60 mg dose cohorts) completed dosing from days 1 to 13 but did not receive the day 14 dosing. As both subjects completed follow-up blood sampling, data from these two subjects were included in pharmacokinetic and biomarker data analyses.

## Results

### Subject demographics

As shown in Table 1, the treatment groups were similar in demographic characteristics. Of the 80 healthy subjects enrolled in the study, 58.8% were male and 51.3% were female. The majority (90%) of the subjects was White, and the mean age for all subjects was 29.1 years.

### Pharmacokinetics of pegvisomant

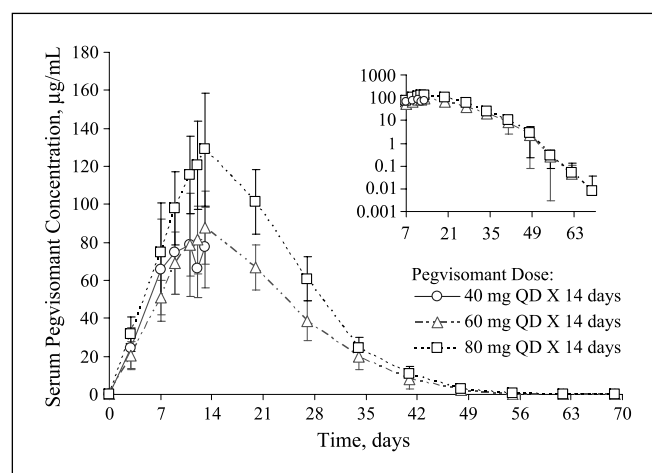
As shown in Fig. 1, mean serum pegvisomant concentrations increased steadily during the 14 days of daily s.c. pegvisomant

injections. The maximal concentrations were generally observed at the end of 14 days of dosing. The substantial accumulation in exposure after repeated daily dosing is consistent with the relatively long  $t_{1/2}$  of pegvisomant at these dose levels.

The mean systemic exposure variables ( $C_{\text{trough, day14}}$  and  $\text{AUC}_{0\text{-day14}}$ ) increased with dose (Fig. 1; Table 2). There was a considerable overlap in systemic pegvisomant exposures at the three dose levels evaluated, possibly due to the narrow dose range and absorption variability after s.c. injection of relatively large volumes at multiple sites.

### Effects on IGF-I

**Total IGF-I.** Figure 2 shows the time course of plasma total IGF-I concentrations as a percentage of the respective pretreatment baseline in subjects receiving pegvisomant or octreotide treatment. Daily s.c. dosing of pegvisomant for 14 days led to substantial suppression of total IGF-I at all three dose levels. The maximal suppression seemed to be reached at the end of pegvisomant dosing and was sustained for ~3 weeks (21 days) after the end of dosing. In most of the subjects, the total IGF-I concentrations slowly returned to pretreatment levels in ~5 weeks (day 56) after the last dose. There was no apparent



**Fig. 1.** Serum concentration-time profiles of pegvisomant following daily s.c. pegvisomant administration to healthy subjects for 14 d. Points, mean; bars, SD. Inset, part of the concentration-time profiles in logarithmic scale.



**Table 2.** Pharmacokinetic variables of pegvisomant after daily s.c. pegvisomant administration to healthy subjects for 14 days

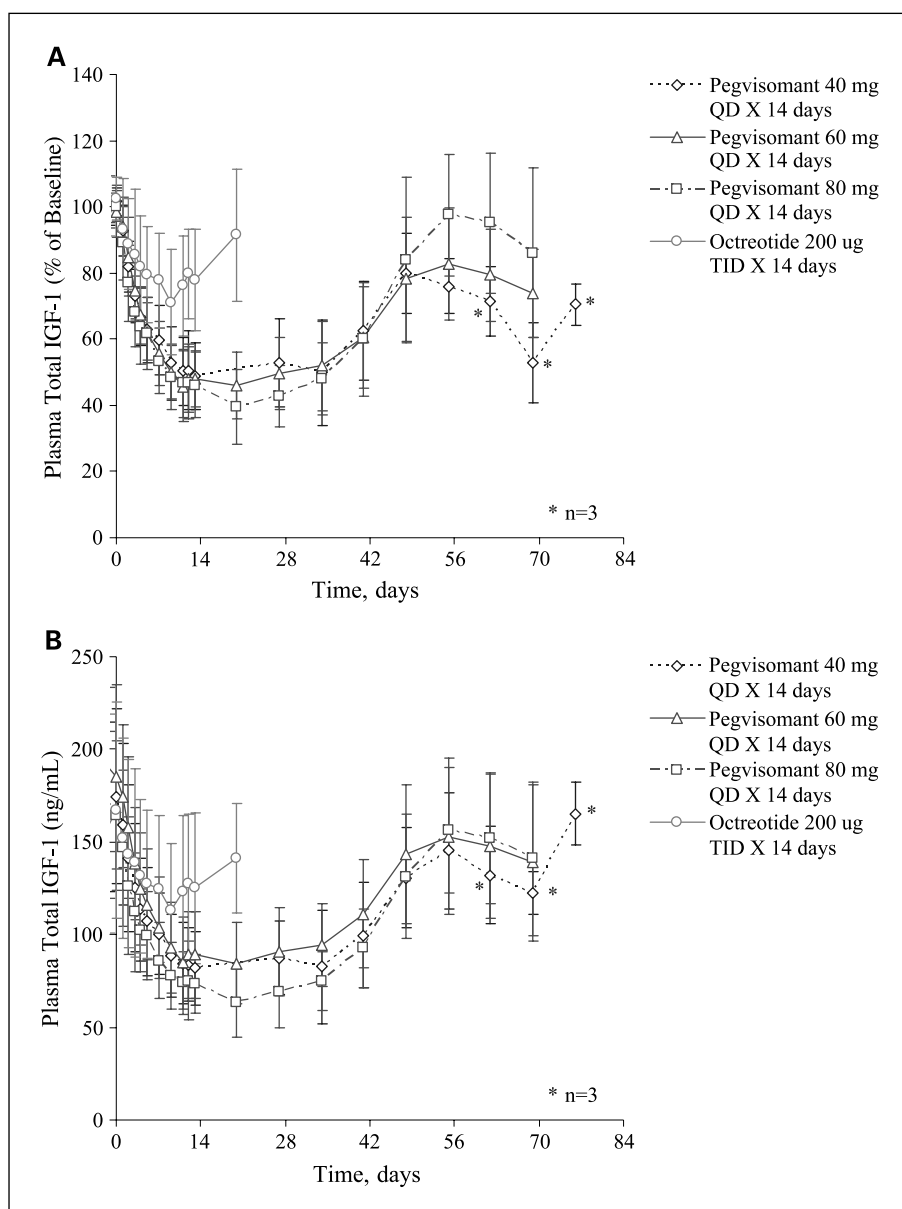
Dose (mg/d)	n	Variables (mean ± SD)			
		$C_{\text{trough,day14}}$ (µg/mL)	$AUC_{0\text{-day14}}$ (µg·h/mL)	$AUC_{0\text{-inf}}$ (µg·h/mL)	$t_{1/2}$ (h)
40	17	77.3 ± 21.2	15,668 ± 4,286	NC*	NC*
60	18	87.8 ± 19.5	14,544 ± 2,781	43,866 ± 7,957	64.7 ± 10.9
80	16	129 ± 29.7	21,337 ± 3,763	65,651 ± 10,128	93.8 ± 74.9

Abbreviation: NC, not calculated.

\*Blood samples for pharmacokinetics were not collected after the last dose.

indication of rebound phenomena in the recovery of total IGF-I concentrations. Octreotide at 200 µg TID for 14 days also reduced total IGF-I concentrations, with a maximal inhibition observed at the end of dosing. However, the suppression in

total IGF-I produced by octreotide was considerably less in magnitude and shorter in duration compared with those by pegvisomant. The total IGF-I started to return toward the pretreatment baseline immediately after octreotide dosing



**Fig. 2.** Time course of mean plasma total IGF-I concentrations after s.c. administration of pegvisomant QD or octreotide TID to healthy subjects for 14 d. *A*, total IGF-I concentrations were expressed as percentage of the pretreatment baseline, which is average of the total IGF-I concentrations measured on day -1 and day 1 before the first dose. *B*, IGF-I in absolute concentrations. Points, mean; bars, SD.

**Table 3.** Plasma total IGF-I and IGFBP-3, and IGF-I/IGFBP-3 ratio (mean  $\pm$  SD) at baseline and after treatment with pegvisomant or octreotide

Biomarker	Treatment			
	Pegvisomant (mg/d $\times$ 14 d)			Octreotide ( $\mu$ g TID $\times$ 14 d)
	40	60	80	200
Total IGF-I				
Baseline (ng/mL)	169 $\pm$ 46	189 $\pm$ 44	165 $\pm$ 45	160 $\pm$ 59
Nadir during treatment (ng/mL)	71 $\pm$ 17	75 $\pm$ 20	61 $\pm$ 16	102 $\pm$ 32
Maximum suppression (%)	57 $\pm$ 9	60 $\pm$ 7	62 $\pm$ 9	36 $\pm$ 16
Duration of suppression (days after the last dose)	>35	>35	>35	~7
IGFBP-3				
Baseline (ng/mL)	2,161 $\pm$ 454	2,169 $\pm$ 311	2,043 $\pm$ 335	1,942 $\pm$ 516
Day 14 (ng/mL)	1,415 $\pm$ 307	1,430 $\pm$ 235	1,177 $\pm$ 217	1,702 $\pm$ 441
Total IGF-I/IGFBP-3 ratio				
Baseline (ng/mL)	0.082 $\pm$ 0.026	0.086 $\pm$ 0.014	0.081 $\pm$ 0.018	0.086 $\pm$ 0.026
Day 14 (ng/mL)	0.059 $\pm$ 0.014	0.062 $\pm$ 0.014	0.064 $\pm$ 0.015	0.078 $\pm$ 0.034

stopped. In terms of maximal suppression, pegvisomant at 40, 60, and 80 mg QD doses maximally reduced the mean total IGF-I concentrations by 57%, 60%, and 62% (Table 3). In contrast, octreotide at 200  $\mu$ g TID maximally inhibited the mean total IGF-I by 36% (Table 3).

**Free IGF-I.** Figure 3 shows that both pegvisomant and octreotide decreased free IGF-I concentrations, and the effect was associated with a considerable intersubject variability. The maximum suppression was comparable between pegvisomant and octreotide, with the mean values ranging from 24% to 33%; yet, it is noticeable from Fig. 3 that the decrease in free IGF-I produced by pegvisomant was more prolonged in duration compared with that by octreotide. The decrease in free IGF-I induced by pegvisomant is relatively smaller compared with that in total IGF-I, suggesting an increase in the IGF-I free fraction, possibly as a result of pegvisomant-induced decrease in IGFBP-3 (described in the following).

### Effects on IGFBP-3

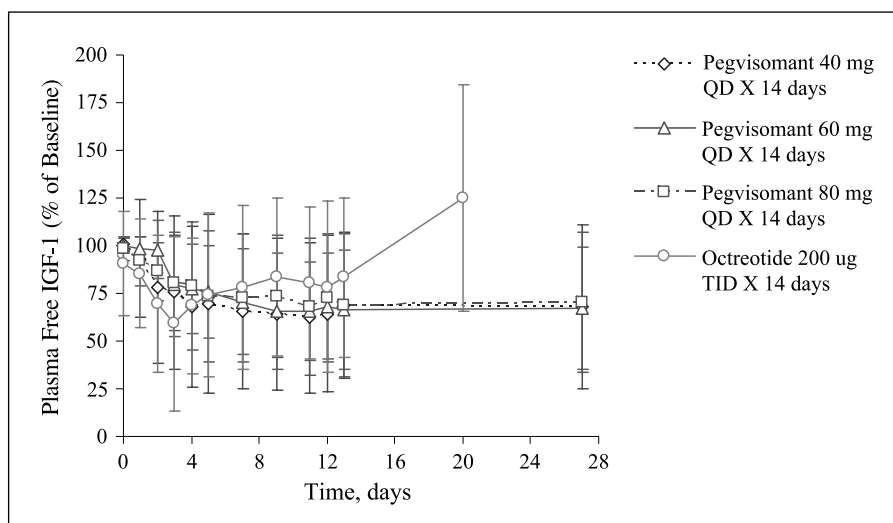
Figure 4 shows the profiles of mean IGFBP-3 as percentage of baseline in subjects receiving pegvisomant or octreotide. Pegvisomant decreased IGFBP-3 concentrations over the entire

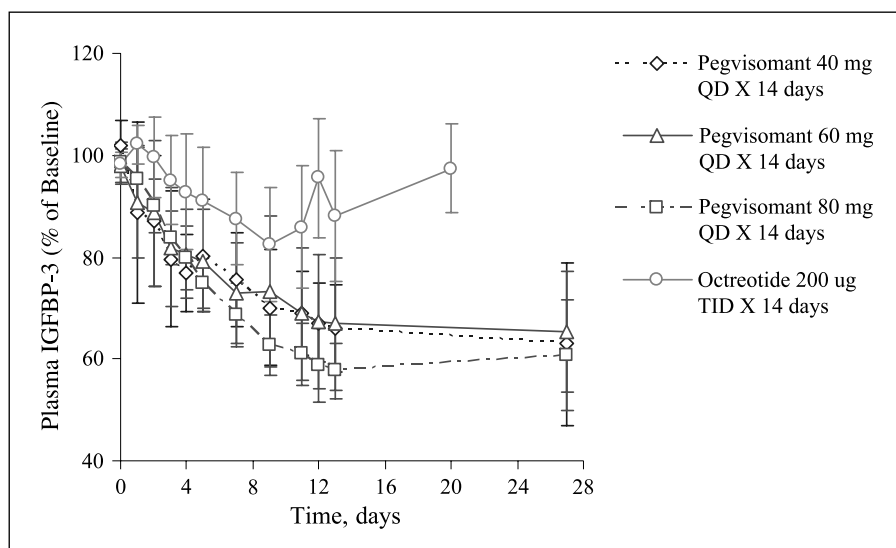
14-day dosing period. The maximum suppression lasted for at least 2 weeks after the last dose. In comparison, octreotide led to a much shorter period of suppression in IGFBP-3, and the IGFBP-3 concentrations returned to baseline levels within 1 week after the last dose. The mean of maximal percentage inhibition in IGFBP-3 ranged from 38% to 46% for the three dose levels of pegvisomant, which was almost twice that observed for octreotide. In addition, pegvisomant also reduced the total IGF-I/IGFBP-3 ratio by an average of 21% to 28%, whereas octreotide had no apparent effect on the ratio (Table 3). Being the most abundant form of at least six IGFBPs, IGFBP-3 is regulated by GH and IGF-I. It is possible that IGFBP-3 serves as a feedback mechanism to buffer the change in free IGF-I when total IGF-I concentration changes.

### Effects on IGF-II

Pegvisomant showed substantial inhibitory activity toward plasma IGF-II concentrations (Fig. 5). The inhibition cumulated with each dose of pegvisomant, and the maximum inhibition lasted for at least 2 weeks after the last dose. Inhibition in IGF-II ranged from 29% to 35% for the three dose levels of pegvisomant. There was no apparent trend of

**Fig. 3.** Time course of mean plasma free IGF-I concentrations after s.c. administration of pegvisomant QD or octreotide TID to healthy subjects for 14 d. Free IGF-I concentrations were expressed as percentage of the pretreatment baseline, which is average of the free IGF-I concentrations measured on day -1 and day 1 before the first dose. Points, mean; bars, SD.





**Fig. 4.** Time course of mean plasma IGFBP-3 concentrations after s.c. administration of pegvisomant QD or octreotide TID to healthy subjects for 14 d. IGFBP-3 concentrations were expressed as percentage of the pretreatment baseline, which is average of the IGFBP-3 concentrations measured on day -1 and day 1 before the first dose. Points, mean; bars, SD.

dose-response relationship with respect to IGF-II suppression. With octreotide, there was no IGF-II suppression during dosing, and IGF-II concentrations mostly fluctuated around the pretreatment baseline levels.

**Effects on GH**

In most of the subjects receiving pegvisomant treatment, the GH concentrations were elevated up to 2 weeks after the last dose (data not shown). The mean of maximum increase ranged from 12- to 28-fold at the three dose levels. There were considerable intrasubject and intersubject variability in GH concentrations. The increase in GH concentrations was likely due to the decreased IGF-I concentration and subsequent release of the feedback inhibition on GH production by IGF-I. In subjects receiving octreotide, the GH concentrations remained mostly below the LLOQ as expected.

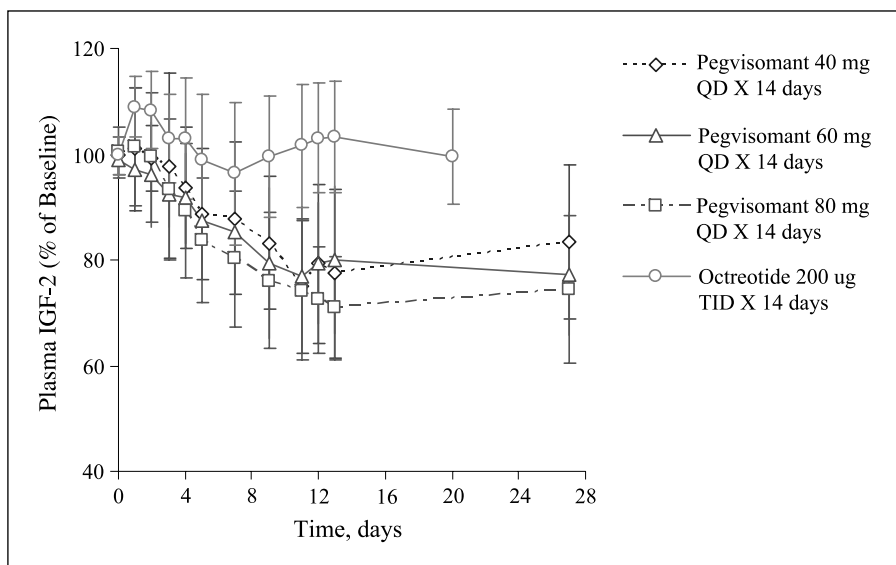
**Biological variability in biomarkers**

Table 4 summarizes the intrasubject and intersubject biological variability in total IGF-I, free IGF-I, IGF-II, and

IGFBP-3 over a 9-week period in untreated healthy subjects. There was a relatively low intrasubject variability (<10%) in these biomarkers. The intersubject variability in the untreated subjects was, in general, comparable with those in pegvisomant- or octreotide-treated subjects. The plasma concentrations of GH were below the LLOQ in most subjects; thus, estimation of variability was not possible.

**Safety assessment**

Pegvisomant is generally well tolerated in healthy subjects after daily s.c. administration at dose levels up to 80 mg for 14 days. There were no deaths or serious AEs. No Common Toxicity Criteria grade 4 AEs were observed. Four subjects treated with pegvisomant (two at the 40-mg dose level and one each at 60- and 80-mg dose levels) discontinued or withdrew consent due to AEs. AEs were similar to those reported in previous studies for acromegalic and diabetic patients treated with Somavert. As listed in Table 5, the most common AEs reported in pegvisomant-treated subjects included injection site bruising (*n* = 27), headache (*n* = 22), and fatigue (*n* = 12). As



**Fig. 5.** Time course of mean plasma IGF-II concentrations after s.c. administration of pegvisomant QD or octreotide TID to healthy subjects for 14 d. IGF-II concentrations were expressed as percentage of the pretreatment baseline, which is average of the IGF-II concentrations measured on day -1 and day 1 before the first dose. Points, mean; bars, SD.

**Table 4.** Intrasubject and intersubject biological variability in biomarkers in untreated subjects

Biomarker	Mean intrasubject CV%	Intersubject CV% of individual mean values
Total IGF-I	9.2	31
Free IGF-I	9.0	72
IGF-II	6.2	12
IGFBP-3	6.0	16

in prior studies, the AEs were mild to moderate in severity and generally without a clear relationship to dose.

In octreotide-treated subjects, one AE of headache was a Common Toxicity Criteria grade 3 and all other AEs were Common Toxicity Criteria grade 1 or 2. The most common AEs observed in octreotide-treated subjects were loose stools and flatulence (15 subjects each), and abdominal pain not otherwise specified ( $n = 10$ ).

There were no clinically significant treatment group differences or apparent treatment-related change in postdose clinical laboratory abnormalities. At screening and baseline, the four treatment groups were not clinically significantly different in blood pressure, pulse, respiration, or temperature. Pegvisomant treatment produced no consistent or clinically significant changes in vital signs, whereas treatment with octreotide produced consistent, modest decreases in blood pressure and pulse.

## Discussion

GHR-mediated signal transduction pathways have been implicated in tumor pathogenesis and progression for a number of common cancers. Through binding to the GHR

with high affinity and preventing the receptor dimerization, pegvisomant blocks GHR-mediated signaling, leading to suppression of circulating IGFs (IGF-I and IGF-II) and regulation of other downstream molecules involved in the GH axis (2, 38–40). The present study showed that pegvisomant at s.c. doses higher than those used for treatment of acromegaly could effectively suppress the GH axis, with the magnitude and duration of suppressive effects considerably exceeding those of octreotide. These results provide evidence in favor of further testing the hypothesis that pegvisomant, through blocking the GHR-mediated signal transduction pathways, could be effective as a cancer therapy.

Although pegvisomant substantially inhibited circulating IGF-I concentrations at all three dose levels evaluated, the 2-fold increase in pegvisomant doses only increased the degree of maximum IGF-I suppression by ~5%. The magnitude of IGF-I suppression exceeded those previously observed in healthy subjects after a single s.c. injection at doses up to 1 mg/kg, where IGF-I was inhibited by as much as nearly 50% (38–40). The greatest suppression was close to 75%, as observed in several subjects receiving pegvisomant at 60- and 80-mg doses. It is known that circulating IGF-I is primarily produced in the liver as a result of GH stimulation of the *IGF-I* gene promoter. In addition to the liver, other organs are also known to synthesize IGF-I as a paracrine or autocrine growth factor, although the IGF-I not immediately bound at the organ site does comprise ~20% to 25% of the circulating total IGF-I (34). IGF-I synthesis in some of these organs may be under the control of GH as well as other factors such as sex hormones (22, 34). Studies in mice have shown that deletion of *IGF-I* gene in the liver resulted in a 70% decrease in circulating IGF-I concentrations and the remaining plasma IGF-I responded poorly to GH (41). Thus, the present study may also indicate that the suppression of circulating IGF-I achieved

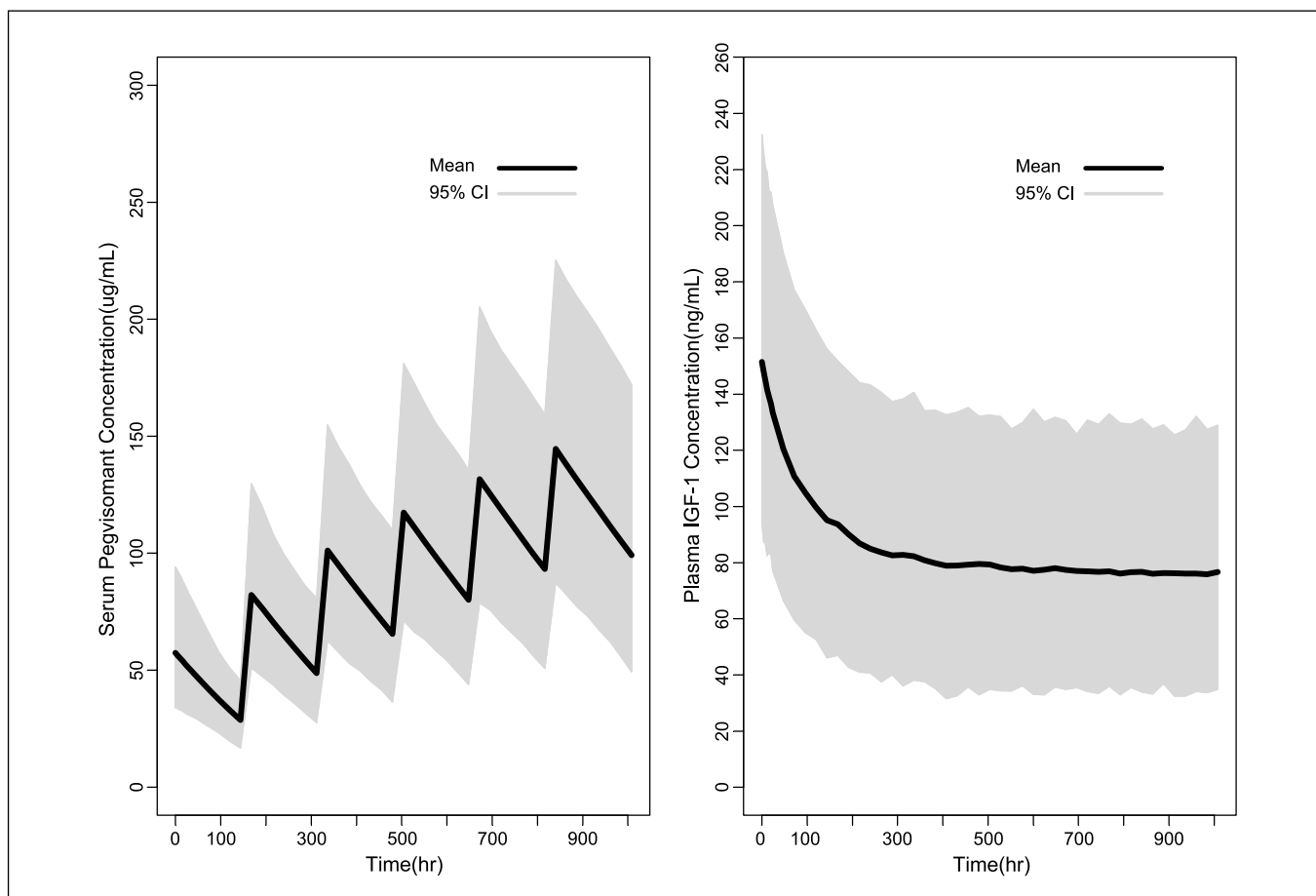
**Table 5.** Common AEs and frequency in subjects receiving pegvisomant or octreotide

Most common AEs	No. of subjects with grade 1 or 2 AEs [total N of AE (n of treatment-related AE)]			
	Pegvisomant ( $\mu\text{g/d} \times 14 \text{ d}$ )			Octreotide ( $\mu\text{g TID} \times 14 \text{ d}$ )
	40 (N = 18)	60 (N = 18)	80 (N = 18)	200 (N = 18)
Abdominal distension	—	—	—	2 (2)
Abdominal pain	2	1	—	17 (7)
Diarrhea	2	—	—	3 (3)
Dry mouth	2	1	2 (2)	—
Flatulence	1	—	—	15 (15)
Loose stools	—	1	—	15 (15)
Nausea	1	—	2 (1)	4 (3)
Fatigue	7	4	2 (2)	2
Injection site bruising	12 (12)	6 (6)	9 (9)	5 (5)
Injection site reaction*	6 (6)	8 (6)	3 (3)	11 (11)
Injection site urticaria	1	—	—	2 (2)
Arthralgia	2	1	1	—
Myalgia	2	—	—	—
Pain (back)	2	1	—	2
Dizziness	3	—	—	1 (1)
Headache	8 <sup>†</sup>	9	5 (2)	7 <sup>†</sup>
Nasopharyngitis	3	3	1	—
Pruritis	1	2 (2)	2 (1)	—
Rash	1	—	5 (5)	2

\* $n \geq 1$ : pain, swelling, erythema, or pruritis.

<sup>†</sup> One patient with grade 3.





**Fig. 6.** Monte Carlo simulation of concentration-time profiles of serum pegvisomant and plasma IGF-I after weekly i.v. administration of 150 mg pegvisomant. Simulation was based on population pharmacokinetic/pharmacodynamic modeling of pegvisomant and IGF-I concentration-time data from the present study. S.c. bioavailability of 57% as determined in a previous study was used in the simulation. The means and 95% confidence intervals (95% CI) were based on simulation of 1,000 subjects with baseline IGF-I concentrations typical of healthy subjects enrolled in the present study.

by pegvisomant is approaching an upper limit, and the residual circulating IGF-I is no longer sensitive to modulation of the GH control.

It is noteworthy to point out that pegvisomant may exert its anticancer activity through dual mechanisms, involving blockade of both the endocrine and paracrine/autocrine effects of GH. Although most of the normal biological actions of GH are mediated through endocrine stimulation of IGF-I production, GH is known to have direct paracrine/autocrine effects in local tissues independent of circulating IGF-I. These paracrine/autocrine effects of GH may also have important implications in tumor growth and progression, as shown by recent findings that autocrine GH promotes carcinogenesis and invasiveness of mammary carcinoma cells (17, 42). The dual effects of pegvisomant on both GH and IGF-I signaling in target tissues have been shown in mice, in which pegvisomant blocked the phosphorylation of Janus-activated kinase 2/signal transducers and activators of transcription 5 (GHR-mediated) and phosphorylation of IGF-I receptor/insulin receptor substrate-1 (IGF-I-mediated) within mammary glands, leading to regression of breast cancer xenografts (32). The ability of pegvisomant to block the membrane GHR signaling in local tissues, in addition to its activity in lowering circulating IGF-I concentrations, offers

an opportunity to evaluate the effectiveness of comprehensive GH signaling blockade in cancer therapy.

Because of its relatively long  $t_{1/2}$ , pegvisomant resulted in prolonged suppressive effects on the GH axis. The sustained duration in GHR antagonism implies the possibility of less frequent dosing with pegvisomant in therapeutic settings. Indeed, a Monte Carlo simulation based on population pharmacokinetics/pharmacodynamics modeling of the pegvisomant and total IGF-I concentration-time data from the present study indicated that weekly i.v. administration of pegvisomant at 150 mg would lead to almost complete GHR antagonism, as indicated by sustained suppression of IGF-I to a similar degree produced by the 80 mg daily s.c. dose (Fig. 6; ref. 43). In this simulation, a s.c. bioavailability of 57%, as determined from a previous study with the 20 mg s.c. dose and 10 mg i.v. dose (44), was used. With this assumption, the 150 mg weekly i.v. dose would lead to a maximal serum concentration similar to that achieved at the end of 14 days of s.c. dosing at 80 mg, and a systemic AUC <50% of that from daily s.c. doses at 80 mg during 1 week of dosing. Also, the 150 mg weekly i.v. dose in humans is <10% of the human equivalent dose of the no-observed-adverse-effect-level observed in a 4-week monkey toxicity study in which i.v.

pegvisomant was well tolerated at biweekly doses up to 40 mg/kg (data not shown).<sup>1</sup> Thus, the weekly i.v. administration may be a viable regimen to be evaluated in further clinical trials of pegvisomant in cancer patients.

In summary, daily s.c. administration of pegvisomant at 40, 60, and 80 mg for 14 days induced substantial and sustained suppression in IGF-I, IGF-II, IGFBP-3, and free IGF-I. The

maximum IGF-I suppression is considerably more consistent and of longer duration for pegvisomant compared with that for octreotide. The therapeutic implications of pegvisomant-induced suppression of GH signaling in anticancer treatment need to be investigated.

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<sup>1</sup>Pfizer internal study report.

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