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Pharmacokinetically Guided Phase 1 Trial of the IGF-1 Receptor Antagonist RG1507 in Children with Recurrent or Refractory Solid Tumors

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Abstract

Purpose—This pediatric phase I study was designed to identify the doses of RG1507, a monoclonal antibody against the Type 1 Insulin-like Growth Factor Receptor (IGF1R), that achieve exposures equivalent to those achieved in adults at recommended doses.

Experimental Design—Children with relapsed or refractory solid tumors were treated using the same doses and administration schedules of RG1507 [3 and 9mg/kg/week, and 16 mg/kg every 3 weeks (q3W)] as those studied in adults. Detailed pharmacokinetic (PK) sampling was performed after the 1st dose; selected peak and trough levels were subsequently obtained. Target exposures were •85% of mean areas under concentration x time curves (AUCs) in adults at doses of 9 mg/kg/week and 16 mg/kg q3W. A maximum tolerated dose could be identified if dose-limiting toxicities (DLT) occurred.

Results—Thirty-one evaluable patients ages 3–17 years were enrolled at 3 mg/kg/week (n=3), 9 mg/kg/week (n=18), or 16 mg/kg q3W (n=10). There were no DLTs. At 9 mg/kg/wk the mean AUC_{0–7d} (21,000 mcg•h/mL) exceeded the target (16,000 mcg•h/mL). At 16 mg/kg q3W, the mean AUC_{0–21d} (70,000 mcg•h/mL) exceeded the target (59,400 mcg•h/mL). Clearance normalized to body weight was age dependent. There were no objective responses. Seven patients had stable disease for >12 weeks, including two patients with osteosarcoma with stable disease for 52+ and 78+ weeks.

Conclusions—The recommended doses of RG1507 in children with solid tumors are 9 mg/kg/week and 16 mg/kg q3W. This flexible design is well-suited for trials of agents associated with limited toxicity.

INTRODUCTION

RG1507 is a fully human monoclonal antibody directed against the Type 1 Insulin-like Growth Factor Receptor (IGF-1R). RG1507 binding results in endosomal degradation of IGF-1R and inhibition of receptor-mediated signaling, which plays an important role in survival, proliferation, and metastasis of neuroblastoma, Ewing family tumors, rhabdomyosarcoma, and Wilms tumor.(1–11) Inhibition of IGF-1R signaling reduces tumor growth in preclinical models of childhood cancers.(12–14)

RG1507 was well tolerated in adults, and maximum tolerated doses (MTD) were not reached in phase 1 trials. The recommended doses of RG1507 (9 mg/kg weekly [qW] and 16 mg/kg every 3 weeks [q3W]) were based on pharmacokinetic (PK) modeling that demonstrated trough concentrations exceeding concentrations required to saturate RG1507 binding to IGF-1R.(15) These concentrations were associated with antitumor activity in preclinical models, and objective responses were observed in adults.(15)

These data suggested that using a conventional pediatric phase 1 trial design to define a MTD of RG1507 in children would not be rational. We instead designed a study to identify the RG1507 dose that achieved an area under the serum concentration-time curve (AUC) equivalent to that achieved in adults at recommended doses. This flexible trial design could also define an MTD if unexpected dose-limiting toxicities (DLT) occurred.

PATIENTS AND METHODS

Trial design

This open-label, multi-center pediatric phase I trial of RG1507 used the same doses and administration schedules (3 and 9mg/kg qW, and 16 mg/kg q3W) as those studied in adults. The primary objective was to determine the RG1507 doses that would achieve mean serum drug exposures (AUCs) •85% of mean AUCs in adults at doses of 9 mg/kg qW and 16 mg/kg q3W. The MTD could be determined if DLT was observed before the primary pharmacokinetic endpoint was reached. The trial design algorithm is shown (Figure 1). Toxicity, pharmacokinetics, and response were also evaluated. Intra-patient dose escalation was not permitted. A cycle was 21 days for both schedules. There was no limit on the number of cycles that could be delivered.

The first 3 children received 3 mg/kg of RG1507 qW. The mean AUC_{0-7d} in these patients was compared to the target AUC_{0-7d} of 16,000 mcgoh/mL (85% of 18,700 mcgoh/mL, the mean AUC_{0-7d} documented in the first cohort of 18 adults treated with 9 mg/kg qW).(15) If the mean AUC_{0-7d} in the first 3 children exceeded the target AUC_{0-7d} in the absence of DLT, the dose level was expanded to 8 patients, including •3 patients ages 2–11 years and •3 patients ages 12–17 years. If the mean AUC_{0-7d} in this expanded cohort exceeded the target AUC_{0-7d} , this dose level would be designated the optimal weekly dose in children, with a

planned expansion to study 6 children each in the 2–6, 7–11, and 12–17 years age groups. If the mean AUC_{0-7d} in the first 3 children or in the expanded cohort were below the target AUC_{0-7d} in the absence of DLT, the dose would be escalated. If the target AUC_{0-7d} was not achieved with 9 mg/kg, additional dose levels could be derived using:

$$Dose\ level\ 3 = \frac{18,700\ mcg \bullet h/mL}{AUC_{0-7d}\ at\ 9mg/kg} \bullet 9mg/kg$$

If DLT were observed in 1 of 3 patients at a dose level, up to 3 additional patients would be treated at the same dose. If •33% of patients experienced DLT, an MTD rather than a pharmacokinetic-determined optimal dose would be identified. The MTD was defined as the highest dose level at which <33% of patients in an expanded cohort experienced DLT. The same design was used to determine the optimal pediatric dose on the q3W schedule. The starting dose was the adult recommended dose of 16 mg/kg/dose. The target AUC_{0-21d} was 59,400 mcgoh/mL (85% of the mean AUC_{0-21d} [69,900 mcgoh/mL] in adults receiving 16 mg/kg).

Patient eligibility

Patients 2 and <18 years of age with measurable or evaluable, relapsed or refractory solid tumors (including primary brain tumors) were eligible. Participation in pharmacokinetic studies was required as this was a primary study endpoint. Other requirements were recovery from acute toxic effects of prior therapies, Karnofsky or Lansky performance score >60, neutrophils (ANC) $1.5 \times 10^9/L$, platelets $100 \times 10^9/L$, age-adjusted normal serum creatinine or clearance $60\ mL/min/1.73m^2$, total bilirubin $1.5 \times$ normal, transaminases $2.5 \times$ normal, and left ventricular shortening fraction 28% . Patients must not have received myelosuppressive therapy within 3 weeks, investigational agents or monoclonal antibodies within 30 days, localized radiotherapy within 2 weeks, radiotherapy to 25% of marrow-rich areas within 4 weeks, retinoids within 7 days, or colony stimulating factors within 10 days of study entry. Prior treatment with anti-IGF-1 receptor antibodies was not permitted. Patients were eligible if 2 months had elapsed since autologous stem cell transplantation or 6 months since allogeneic transplantation, if immunosuppressive therapy had been discontinued 30 days prior to study entry and there was no evidence of active graft-versus-host disease. Patients with central nervous system metastases were eligible if lesions were previously resected or radiated, if corticosteroids had not been administered for 2 weeks, and if neurological deficits were stable for 4 weeks.

Patients with previous hypersensitivity reactions to components of RG1507, prior hypersensitivity reactions to monoclonal antibodies, severe uncontrolled systemic disease, or fever within 3 days of initiation of RG1507 therapy were not eligible. Pregnant or breastfeeding patients, those with known HIV or hepatitis B or C, and those with diabetes mellitus were excluded. This trial was approved by institutional review boards of participating institutions; written informed consent was obtained from patients/legal guardians.

Drug administration

RG1507 derived from murine SP2/0 cell material (F. Hoffmann-La Roche) was diluted with normal saline to a concentration 0.2 mg/mL and administered intravenously over 90 (first dose) or 60 minutes (subsequent doses).

Toxicities

Toxicities were graded according to NCI Common Terminology Criteria for Adverse Events version 3.0. DLT was defined as any non-hematologic, drug-related toxicity grade 3 occurring in the first cycle of therapy, with the exception of nausea, vomiting and diarrhea 24 hours or hypersensitivity reactions occurring during drug infusion. Other DLT included grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring platelet transfusion, grade 4 neutropenia 72 hours duration, grade 3 febrile neutropenia, or treatment delay >14 days due to persistent grade 2 toxicities other than fatigue. Patients with DLT could be re-treated at the next lower dose level. Patients who experienced non-dose-limiting toxicity could be re-treated after resolution of toxicity to grade 1 or baseline.

Pretreatment and follow up studies

At the start of each cycle, histories and physical examinations were done. Complete blood counts, glucose (fasting at screening), electrolytes, phosphorous, calcium, transaminases, lactate dehydrogenase, alkaline phosphatase, albumin, bilirubin, total protein, blood urea nitrogen, and creatinine were obtained at baseline, weekly during the first 2 cycles (qW) or first cycle (q3W), and before subsequent cycles. Pregnancy tests for females of childbearing potential and urinalyses were obtained 7 days prior to the first dose and every 12 weeks. Organ system function requirements were to be met prior to initiation of each cycle of therapy. Triplicate electrocardiograms were performed at least 1 minute apart prior to and immediately following dose 1 and the week 6 (qW) or week 7 (q3W) doses. Sera for detection of Human Anti-Human Antibodies (HAHA) were obtained prior to the first, fourth and tenth (qW) or first, second and fourth (q3W) doses and at follow-up. Disease assessments were 14 days before the first dose and every 6 weeks thereafter. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors criteria.(16) Expression of IGF-1R, pAKT, pErk and PTEN in archival tumor tissues was assessed by immunohistochemical staining (results in Supplemental Table 1).

Serum Pharmacokinetic Sampling and RG1507 Assay

This trial studied the same doses and schedules of RG1507, collected serum samples for pharmacokinetics at the same time points, and measured serum RG1507 concentrations using the same assay method as the adult trials to allow for meaningful comparisons of data. Blood (2 mL) was collected from a site separate from the drug infusion prior to the first dose, at end of infusion, 6, 24, 48, 72, and 168 h after the start of the 90 min infusion for the qW schedule. For the q3W schedule, additional samples were obtained at 336 and 504 hours. Trough blood samples were drawn prior to the 4th, 6th, 8th, and 10th doses on the qW schedule and prior to the 3rd and 4th doses on the q3W schedule. Samples were allowed to clot for 30 min; serum was separated by centrifugation and frozen. RG1507 was quantified in serum using an ELISA assay (25 ng/mL lower limit of quantification).(15)

Pharmacokinetic and Pharmacodynamic Analyses

RG1507 serum concentration-time data were analyzed using non-compartmental methods. End of infusion samples estimated the peak concentration (C_{max}). Area under the concentration curve to the last measured time point (AUC_{0-last}) was calculated with the linear trapezoidal method and extrapolated to infinity ($AUC_{0-\infty}$) by adding the final measured serum concentration divided by the terminal rate constant, derived from the slope of the natural log-transformed concentrations and times on the terminal elimination phase of the decay curve. The half-life ($t_{1/2}$) was calculated by dividing 0.693 by the terminal rate constant. Clearance (CL) equaled dose/ $AUC_{0-\infty}$, and volume of distribution at steady state ($V_{d_{ss}}$) and mean resident time (MRT) were calculated from the area under the moment curve ($AUMC_{0-\infty}$). Accumulation of RG1507 was assessed from trough concentrations.

Serum levels of total IGF-1 were analyzed by ELISA (DSL-10-5600 Active® IGF-I ELISA Kit) according to the manufacturer's instructions. Sera were collected prior to the first dose, at end of infusion, at 6, 24, and 48 h after the infusion for both schedules. For the qW schedule, samples were also drawn prior to dosing at weeks 2, 6, and 10. For the q3W schedule, additional samples were obtained on days 8 and 15 of cycle 1, and prior to the 2nd, 3rd, and 4th drug doses.

RESULTS

Patient Characteristics

Thirty-four patients ages 3–17 years were enrolled at 3 mg/kg qW (n=3), 9 mg/kg qW (n=19), or 16 mg/kg q3W (n=12). Thirty patients completed pharmacokinetic sampling and were evaluable for the primary endpoint; 31 patients were evaluable for toxicity. One patient on each schedule developed disease progression prior to completion of the first cycle of therapy and one patient on the q3W schedule did not receive study drug. Patient characteristics are shown (Table 1).

Toxicity

All drug-related toxicities were grade 2; there were no dose-limiting toxicities and MTD was not defined. Drug-related toxicities reported during cycle 1 are shown (Table 2). There were no treatment interruptions or delays due to toxicity. Toxicities deemed at least possibly related to RG1507 during subsequent cycles included rash, pruritis, nausea, vomiting, anorexia, mucositis, muscle spasms, musculoskeletal pain, fatigue, and neutropenia. Both hyper- and hypoglycemia were observed, but there were no clinical sequelae from altered blood glucose levels and no treatment was required. There was no difference in incidence or severity of toxicities observed on the two dosing schedules. There was no relationship between AUC and severity of toxicities in any patient studied.

Pharmacokinetics and Pharmacodynamics of RG1507

The serum concentration-time profiles of RG1507 at the 3, 9 and 16 mg/kg dose levels are shown (Figure 2). Pharmacokinetic parameters are summarized by dose level and age group (Table 3A). At the starting dose (3 mg/kg qW/wk) the mean AUC_{0-7d} was 5,666 mcg•h/mL, well below the target AUC_{0-7d} of 16,000 mcg•h/mL. The dose was escalated to 9 mg/kg. At

this dose, the mean AUC_{0-7d} (21,000 mcg•h/mL) exceeded the target AUC_{0-7d} ; 15 of 18 patients had an $AUC_{0-7d} > 16,000$ mcg•h/mL. Therefore, 9 mg/kg qW is the recommended dose in children. The mean AUC_{0-21d} after 16 mg/kg q3W (70,000 mcg•h/mL) also exceeded the target AUC_{0-21d} of 59,400 mcg•h/mL. Clearance values from the 10 patients enrolled at the 16 mg/kg q3W dose level were equivalent to clearance values from the 18 patients treated at the 9 mg/kg dose level, therefore additional patients were not enrolled. The recommended dose in children on the q3W schedule is 16 mg/kg/dose. Trough serum concentrations after first and subsequent doses are shown (Table 3B). At the recommended dose levels, trough concentrations exceeded the 20 mcg/mL levels associated with saturation of 90% of IGF-1 receptors. Based on trough concentrations, RG1507 accumulates 3-fold on the qW schedule and 2-fold on the q3W schedule after 9 weeks of treatment.

Within this pediatric population the clearance of RG1507 appeared to be age-dependent (Figure 3). Clearance in younger children normalized to body weight was higher and AUC_{0-7d} was lower in the youngest age group. Two of the 3 patients who did not achieve the target AUC_{0-7d} at the 9 mg/kg/wk dose level were <6 years old, and the single patient who did not achieve the target AUC_{0-21d} at the 16 mg/kg dose level was 8 years old. RG1507 clearance was not age-dependent when normalized to body surface area (Figure 3B).

In all patients studied, total IGF-1 levels were increased by 24 h following dosing and mean values across all patients remained elevated throughout the dosing interval (Supplemental Table). Half of the interpatient variability in total IGF-1 levels was accounted for by patient age (Supplemental Figure 1).

Tumor Response

There were no complete or partial responses to RG1507. However, seven patients had stable disease for >12 weeks. Among the six patients with Ewing sarcoma, two developed disease progression by week 6, two were found to have disease progression at week 12, and two had stable disease through week 12 but progressed by week 18. One patient with epithelioid sarcoma had stable disease for 36 weeks. Two patients with osteosarcoma continue to receive RG1507; one patient has had stable disease for >52 weeks and one has had stable disease for >78 weeks.

Immunogenicity Assays

One patient had positive HAHA at baseline and week 4, and one patient had a positive HAHA at baseline but reverted to negative on study. No hypersensitivity reactions were observed.

DISCUSSION

The clinical development of targeted anticancer agents has highlighted the need for rational dose-finding strategies based on therapeutic endpoints other than toxicity. The MTD of targeted agents may exceed the dose required for therapeutic effect, and dosing at the MTD may unnecessarily expose patients to toxicity. Demonstrating target inhibition in tumor

tissue or achieving drug concentrations known to be inhibitory in preclinical studies are potential alternative endpoints for defining an optimal therapeutic dose.

Dose-finding studies in children usually follow and are informed by trials in adults. Dose escalation trials of cytotoxic agents in children typically start at 80% of the adult MTD and are designed to study fewer dose levels. For agents like RG1507, for which MTD was not defined in adults, alternative endpoints and trial designs are needed for pediatric dose-finding studies. Serial biopsies of solid tumors for pharmacodynamic analyses are not usually feasible in children, and surrogate tissues such as peripheral blood mononuclear cells are not necessarily predictive of drug effects in tumor. In this trial we identified the dose of RG1507 required to achieve a drug exposure in children that was equivalent to the exposure achieved at the recommended dose in adults. Recommended doses in children were 9 mg/kg qW and 16 mg/kg q3W. Both schedules result in trough concentrations that have been associated with receptor saturation; the latter schedule may be more convenient for patients.

This study demonstrates the feasibility of conducting a pharmacokinetically-guided phase I trial of a molecularly targeted drug in children. Preclinical data and pharmacokinetic modeling, which predicted the concentration of RG1507 required to saturate binding to IGF-1R, were used with clinical data from adult studies to select a target drug exposure for this pediatric trial. The success of this design depends on the low degree of inter-patient variability in pharmacokinetics observed in adults and subsequently in children (C.V. 25% for AUC_{0-7d} at 9 mg/kg dose level).

RG1507 was well tolerated at all doses tested. Although subjects were heavily pretreated, neither DLT nor drug-related grade 3 toxicity was observed. Drug-related grade 2 toxicities were easily managed. No cumulative toxicity was observed in patients who received up to 52 weeks of RG1507. Mild hyperglycemia has been reported in patients treated with other antibodies directed against the IGF-1R(17, 18); however, no clinically significant, drug-related hyperglycemia was observed during this trial. Thrombocytopenia has also been observed in adults and in a child treated with IGF-1R inhibitors.(17–19) No drug-related thrombocytopenia was observed in this study. Our findings suggest that RG1507 could be combined with other anti-cancer agents, and could be given safely over an extended time period.

The pharmacokinetic profile of RG1507 in children is similar to that of other monoclonal antibodies and is characterized by a small volume of distribution (mean V_{dss} , 50 mL/kg) and slow elimination (mean clearance, 6.2 mL/d/kg). The drug is measurable in serum throughout the dosing interval on both schedules. Although the lower clearance and longer half-life with the 16 mg/kg q3W dose compared to 9 mg/kg qW could indicate dose-dependent pharmacokinetics, the non-linearity observed more likely results from differences in the duration of sampling (21 vs. 7 days). For direct comparison of exposure and assessment of dose proportionality in children receiving the qW and q3W schedules, the AUC should be calculated to the same last time point. The mean AUC_{0-7d} is 38,000 mcg•h/mL for the 16/mg/kg dose level and 21,000 mcg•h/mL for the 9 mg/kg dose. This 1.8 fold increase in dose and AUC_{0-7d} indicates that the RG1507 exposure in children is dose proportional over the dose range studied. The half-life from the 16 mg/kg dose (mean, 10

days) is likely more accurate than that derived on the weekly schedule because of the longer sampling interval.

We studied 6 children each in 3 age groups at the 9 mg/kg qW dose level, and observed age-dependent drug clearance and lower drug exposures (AUCs) in the youngest patients when the dose was normalized to body weight. Although the mean AUC_{0-7d} in the six children ages 2–6 years exceeded the target AUC_{0-7d} , two of the six had an AUC_{0-7d} below the target. Clearance normalized to body surface area was not age-dependent (Figure 2B). Therefore, we assessed whether dosing RG1507 based on BSA would provide more uniform drug exposure across the pediatric age group. For each of the 18 patients treated at the 9 mg/kg/wk dose level, we derived dose per m^2 by dividing the administered dose by patient BSA and normalized the AUC_{0-7d} to a dose of 300 mg/ m^2 . The mean simulated AUC_{0-7d} for the 2–6, 7–11, and 12–17 year age groups were 23,100, 23,000, and 24,400, respectively. In addition, the AUC_{0-7d} of all six 2–6 year old patients exceeded the target AUC_{0-7d} with 300 mg/ m^2 . Many antibodies and other proteins are dosed based on body weight, but this analysis suggests that dosing based on body surface area, at least with this compound, may be more appropriate in young children.

The trial design used in this study permits dose escalation decision-making based upon either toxicity or pharmacokinetic data. This design is well-suited for trials of agents for which there are robust preclinical pharmacodynamic and pharmacokinetic data and limited toxicity in adults. The design also maintains a focus on patient safety and toxicity monitoring but may facilitate timely dose identification, as it may obviate the need to amend the study protocol if unexpected DLTs are observed. This flexible design may therefore be advantageous for both pediatric and adult phase I trials of new anticancer drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance

Signaling via the Type 1 insulin-like growth factor receptor (IGF-1R) plays an important role in survival, proliferation, and metastasis of several pediatric tumors. This Phase I study was performed to identify the recommended doses of a monoclonal antibody against the IGF1R, RG1507, in children. A flexible trial design was used and two dosing schedules were studied. Drug-related toxicity was minimal; a maximum tolerated dose was not identified. Detailed pharmacokinetic sampling permitted identification of the doses of this agent that achieved exposures similar to those achieved in adults at recommended doses. Age-dependent clearance and lower drug exposures were observed in the youngest patients when dose was normalized to body weight. Dosing of this antibody based on body surface area may be appropriate in young children. Prolonged stable disease was observed in several patients. RG1507 could potentially be combined with other anticancer agents for the treatment of pediatric solid tumors.

Fig 1.

Dose escalation scheme for RG1507 on the weekly dosing schedule. If the target AUC_{0-7d} were not achieved with 9 mg/kg, additional dose levels would have been derived using:

$$Dose\ level\ 3 = \frac{18,700\ mcg \cdot h/mL}{AUC_{0-7d}\ at\ 9mg/kg} \cdot 9mg/kg$$

Fig 2.

Mean serum concentration-time curves for RG1507 at the (A) 3 mg/kg weekly dose level ($n=3$); (B) 9 mg/kg weekly dose level grouped by age into 2–6 yr ($n=6$), 7–11 yr ($n=6$) and 12–17 yr ($n=6$) age groups; and (C) 16 mg/kg every 3 weeks dose level ($n=9$). Note the time scale for A and B is 7 d and for C is 21 d. Error bars are the standard deviation.

Fig 3.

RG1507 clearance, normalized to (A) body weight and (B) body surface area, as a function of age. Clearance normalized to body weight appears to be age-dependent, as 32% of the variation shown can be attributed to weight ($R^2=0.32$) and the relationship between age and clearance is significant ($p=0.001$). When normalized to body surface area, clearance is more uniform across age groups. Only 2% of the variation shown can be attributed to body surface area ($R^2=0.02$) and there is no statistically significant relationship between age and

clearance when dose is normalized to body surface area ($P=0.001$). These data suggest that dosing based on body surface area may yield more uniform drug exposure in children.

Table 1

Patient Characteristics

Characteristic	
Number evaluable for toxicity	31
Number evaluable for pharmacokinetic endpoint	30
Gender	
Male	17
Female	14
Median (range) Age (years),	11 (3–17)
Race	
White	21
Black	4
Hispanic	5
Multiple Race	1
Performance Status (Lansky or Karnofsky)	
90	24
70 – <90	6
60 – <70	1
Tumor Type	
Ewing Sarcoma	6
Rhabdomyosarcoma	5
CNS tumors*	6
Liver tumors^	4
Osteosarcoma	3
Other#	7
Prior Chemotherapeutic Regimens	
2 regimens	12
>2 but 4 regimens	8
>4 regimens	11

* CNS tumors included medulloblastoma, ependymoma (3), atypical teratoid/rhabdoid tumor, and anaplastic astrocytoma

^ Liver tumors included 2 each: hepatoblastoma and hepatocellular carcinoma (fibrolamellar variant).

Other: neuroblastoma, adrenocortical carcinoma (2), Hodgkin's disease, desmoplastic small round cell tumor, epithelioid sarcoma, undifferentiated sarcoma

Table 2

RG1507-related toxicity during cycle 1 by dose level and toxicity

	Dose level (mg/kg/dose)											
	3 (n=3)				9 (n=18)				16 (n=10)			
	Number of Patients with Toxicity Grade During Cycle 1											
Toxicity	1	2	3	4	1	2	3	4	1	2	3	4
Constitutional												
Fatigue					1							
Chills					1							
Gastrointestinal												
Anorexia					1							
Diarrhea					1							
Nausea					2							
Vomiting					1							
Metabolic/Laborator												
Hyperbilirubinemia							1					
Pain												
Extremity			1			1			1		1	*
Axial skeleton											1	*
Chest											1	*
Myalgia					1							
Genitourinary									1			
Cardiovascular												
Hypotension									1			
Pulmonary												
Dyspnea									1			
Dermatology/Skin												

Dose level (mg/kg/dose)												
3 (n=3)			9 (n=18)			16 (n=10)						
Number of Patients with Toxicity Grade During Cycle 1												
Toxicity	1	2	3	4	1	2	3	4	1	2	3	4
Pruritis									1			

* Toxicities occurring in the same patient

Table 3A

Mean (%CV) pharmacokinetic parameters for RG1507 by dose level and age group.

level [mg/kg]	Age group [yr]	n	C _{max} [mcg/ml]	AUC _{0-last} [mcg•h/ml]	AUC _{0-∞} [mcg•h/ml]	T _{1/2} [d]	CL [ml/d/kg]	Vd _{ss} [L/kg]	MRT [d]	C _{min} [mcg/ml]
3	2 to 17	3	71 (27)	5,700 (30)	10,000 (48)	5.5 (27)	8.2 (39)	0.060 (21)	7.8 (27)	22 (44)
9	2 to 6	6	223 (15)	17,000 (11)	30,000 (15)	5.8 (17)	7.3 (14)	0.060 (14)	8.3 (17)	65 (13)
9	7 to 11	6	253 (30)	21,000 (31)	34,000 (29)	5.2 (20)	7.0 (36)	0.052 (45)	7.4 (20)	71 (27)
9	12 to 17	6	292 (15)	25,000 (15)	40,000 (25)	5.1 (27)	5.6 (23)	0.038 (15)	7.2 (28)	87 (21)
16*	2 to 11	4	400 (20)	58,000 (20)	73,000 (19)	9.3 (10)	5.4 (24)	0.068 (25)	13 (11)	48 (18)
16*	12 to 17	5	500 (29)	79,000 (11)	104,000 (12)	10.1 (25)	3.8 (12)	0.054 (23)	15 (24)	69 (33)

* Every 3 week schedule with pharmacokinetic sampling to day 21.
Abbreviations: C_{max}, peak serum concentration; AUC, area under the serum concentration-time curve; T_{1/2}, half-life in serum; CL, clearance; Vd_{ss}, volume of distribution at steady state; MRT, mean residence time; C_{min}, trough serum concentration prior to the second

Trough ($C_{\min}$) RG1507 serum concentrations and serum total IGF levels (expressed as percent change from baseline) following the first and subsequent doses at 9 mg/kg weekly and 16

Table 3B

RG1507				Total IGF	
Dose level [mg/kg]	n	Post-dose number	Mean $C_{\min}$ [mcg/mL]	Mean accumulation index*	% Increase from Baseline
9	18	1	74	-	15
9	16	3	163	2.2	
9	13	5	222	2.8	13
9	8	7	250	3.2	
9	8	9	287	3.4	9
16	9	1	60	-	9
16	6	2	103	1.7	6
16	6	3	118	2	5

* The accumulation index is the ratio of the trough concentration after the second and subsequent doses divided by the trough concentration after the first dose.