CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN-125085/0

Clinical Pharmacology/TOX Review

Avastin (Bevacizumab also known as rhuMab VEGF)

STN# 125085/0

Genentech, Inc.

Indication: Avastin in combination with 5-fluorocil is indicated for the first line treatment for metastatic carcinoma of the colon and rectum.

Clinical Pharmacology & Toxicology Branch, OTRR (HFD-579)

Reviewer: Iftekhar Mahmood, Ph. D.

Assistant to the Director for Pharmacology and Toxicology ODE VI: Martin David Green, Ph. D.

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SUMMARY

New blood vessels are essential for the growth of solid tumors and now it is well recognized that the angiogenic factors are responsible for stimulating new blood vessel formation. Among all the identified angiogenic factors, the most potent is VEGF. It has been shown in nude mice that inhibition of VEGF by anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell line. Rhumab VEGF is a humanized monoclonal IgG1 antibody that competitively inhibits tumor growth in vivo by reducing the formation of new blood vessels thus cutting the blood supply to the tumor. Rhumab VEGF inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells.

AVASTIN (bevacizumab) is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). AVASTIN is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing

AVASTIN consists has a molecular weight of approximately 149,000.

The pharmacokinetics of AVASTIN were characterized in 8 clinical studies from Phase I to Phase III. A ninth study was a population PK study which included data from Phase I to Phase III studies. With the exception of two Phase I studies where frequent blood samples were drawn, the rest of the PK studies were based on sparse sampling, mainly the peak and trough levels. Therefore, the pharmacokinetic parameters generated from these studies should be interpreted with extreme caution. Table 1 summarizes the 8 clinical studies that included pharmacokinetic analysis. The following is the summary of several PK studies submitted in this BLA.

Single Dose

In Phase I study, bevacizumab was given to patients with solid tumors at doses of 0.1, 0.3, 1.0, 3, and 10 mg/kg as a single dose and then 28 days later weekly for three more doses. Bevacizumab plasma concentrations versus time data were fitted to a two-

compartment model. The pharmacokinetics of bevacizumab were linear between 1 to 10 mg/kg. The clearance of bevacizumab ranged from 2.75 to 3.65 mL/day/kg at doses 1 to 10 mg/kg. The estimated mean terminal half-life of bevacizumab at doses> 1 mg/kg ranged from 13 to 15 days by compartmental methods and from 13 to 19 days by non-compartmental methods. Since blood samples were only collected till day 28, this estimate of half-life was considered a preliminary estimate. A population PK study indicated that the mean half-life of bevacizumab was 20 days (from Bayesian estimate individual half-life varied from 13 to 45 days). Following four doses of bevacizumab, the clearance of bevacizumab after the first dose and after all four doses was comparable, without any indication of accumulation. It should be however, noted that the multiple dose was not carried out long enough to determine the accumulation of bevacizumab in the systemic circulation.

Table 1
Summary of Studies of Bevacizumab Providing Pharmacokinetic and Pharmacodynamic Data

	Study, Indication	Regimen: Dose (mg/kg)	Regimen: Frequency	Dose (mg/kg/wk)	Concomitant Chemotherapy	Sampling Scheme Frequency
Phase I	AVF0737g Dose-escalation, solid tumors	0.1, 0.3, 1, 3, 10	Once, then 28 days later, weekly × 3	Varied	None (single agent)	Full profile for all subjects [a]
	AVF0761g, Solid tumors	3	Weekly	3	Doxorubicin, carboplatin/paclitaxel, 5-FU/LV	Full profile for all subjects [a]
Phase II	[redacted]	10	Every 2 weeks	5	None (single agent)	Multiple peaks and troughs for all subjects
	[redacted] Dose-escalation, MBC	3, 10, 20	Every 2 weeks	1.5, 5, 10	None (single agent)	Multiple peaks and troughs for all subjects
	[redacted] Combination, NSCLC	7.5, 15	Every 3 weeks	2.5, 5	Carboplatin/paclitaxel	Multiple peaks and troughs for all subjects
	AVF0780g Combination, CRC	5, 10	Every 2 weeks	2.5, 5	5-FU/LV	Multiple peaks and troughs all subjects
Phase III	[redacted] MBC	15	Every 3 weeks	5	Capecitabine	Multiple peaks and troughs for a subset of subjects
	AVF2107g (Arm 2 and 3) CRC	5	Every 2 weeks	2.5	5-FU/LV/irinotecan, 5-FU/LV	Peaks and troughs at 2 cycles for a subset of subjects

5-FU = 5-fluorouracil; CRC = colorectal carcinoma; HRPC = hormone refractory prostate carcinoma; LV = leucovorin; MBC = metastatic breast carcinoma; NSCLC = non small cell lung carcinoma.

[a] Serial samples collected over 1 month after administration of either first or last dose.

Multiple Dose

Following multiple dosing of 3 to 15 mg/kg every 2 to 3 weeks the clearance ranged from 2.48 to 3.74 mL/day/kg across studies and doses. In Phase II studies ([redacted] and AVF0780g), the serum concentrations of bevacizumab following multiple doses every 2 or 3 weeks were followed for up to 1 year in some subjects. The

time to steady state in these studies was estimated to be about 100 days. The accumulation index was calculated by comparing average bevacizumab trough concentrations at steady state with average trough concentrations following the first dose. The accumulation index was estimated as follows:

Accumulation index = Steady state trough / trough after the first dose.

The expected accumulation index was calculated as follows:

$$\text{Accumulation Index} = 1/1\text{-}e^{-\beta\tau}$$

where β is the elimination rate constant and τ is dosing frequency. The following Table summarizes the accumulation index of bevacizumab.

TABLE 2

Accumulation Index of Bevacizumab

Study	Dose (mg/kg)	Dose Frequency	Average $C_{trough,}$ first (µg/mL)	No. of Subjects with $C_{trough,}$ first	Average $C_{trough,}$ last (µg/mL)	T_{last} (day)	No of Subjects with C_{trough} last	Accumulation Index	Expected Accumulation Index
[redacted]	10	q 2 wk	67.1	15	182	182	5	2.7	2.6
[redacted]	3	q 2 wk	55.5	16	78.4	154	3	1.4	2.6
	10	q 2 wk	79.4	41	229.6	154	8	2.9	2.6
	20	q 2 wk	137.5	16	332.3	154	3	2.4	2.6
AVF0780g	5	q 2 wk	35.4	32	81.7	322	11	2.3	2.6
	10	q 2 wk	59.9	30	169.2	322	10	2.8	2.6
[redacted]	7.5	q 3 wk	31.3	27	58.3	378	4	1.9	1.9
	15	q 3 wk	68.4	31	107.9	378	7	1.6	1.9

C_{trough} = trough concentration.

Interaction of Bevacizumab with other Drugs

The pharmacokinetics of bevacizumab co-administered with other chemotherapeutics were evaluated in one Phase I study, two Phase II studies, and two Phase III studies. The similar values of CL and V_c of bevacizumab across doses and studies when administered as a single agent or in combination suggest that the pharmacokinetics of bevacizumab are not affected by dosing of concomitant chemotherapeutics such as doxorubicin, carboplatin/paclitaxel, 5-FU/leucovorin, capecitabine, and 5-FU/leucovorin/irinotecan. In addition, based on the population PK analysis, there was no difference in clearance of bevacizumab in subjects treated with single-agent bevacizumab and that in subjects treated with bevacizumab in combination

with the bolus-IFL regimen in the pivotal Phase III study in metastatic colorectal cancer (AVF2107g). However, the effect of other co-administered chemotherapies on bevacizumab CL was modest (17%) and may be associated with either the chemotherapy agents or the tumor types. With the exception of SN38 (the active metabolite of irinotecan), the pharmacokinetics of the co-administered chemotherapeutic drugs were not affected by bevacizumab. In Study AVF2107g, irinotecan concentrations were not affected when dosed alone or in combination with bevacizumab. There was a statistically significant 33% increase in exposure to SN38.

(The aforementioned summary on drug interaction is based on the Sponsor's conclusion not necessarily agreed by the reviewer. Overall, the design of the drug interaction studies is inadequate and it is difficult to make any definitive conclusion).

Population Pharmacokinetic study of Bevacizumab

The effects of age, gender, and concomitant administration of chemotherapeutic agents on the pharmacokinetics of bevacizumab were assessed using population PK analysis. The population PK analysis for bevacizumab was based on the pooled datasets from eight clinical studies including two Phase I studies, four Phase II studies, and two Phase III studies in subjects with several types of solid tumors. The analysis included a total of 4629 bevacizumab concentrations for 491 subjects who received IV infusion doses weekly, every 2 weeks, or every 3 weeks at doses ranging from1 to 20 mg/kg. Serum bevacizumab concentration-time data were modeled using a population analysis approach to estimate bevacizumab population PK parameters (mean and intersubject variability) as well as relationships between the PK parameters and various covariates. The best structural model was a two-compartment model with first-order elimination. In the final model, of the 17 covariates tested, body weight, gender, albumin, alkaline phosphatase, SGOT, and chemotherapy were the only covariates that were significantly associated with bevacizumab disposition. Based on the final model, clearance was 0.262 and 0.207 L/day for a typical male and female subject, respectively. The volume of distribution of the central compartment (V_c) was 3.25 and 2.66 L in male and female

subjects, respectively. The estimated half-life was approximately 20 days. Body weight was an important covariate affecting bevacizumab CL and volume. There was no correlation between bevacizumab clearance and age. Gender seems to have impact on clearance and volume. The clearance and volume is 21% and 18% lower in the females than the males, respectively. After correcting for body weight, male subjects had a higher bevacizumab clearance (26%) and a larger Vc (22%) than females. However, this difference may not be of any clinical significance.

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ON ORIGINAL

Recommendation

Every pharmacokinetic study (an exception is population PK) in this submission lacks proper design and sampling scheme. Particularly drug-interaction studies have been poorly designed and blood-sampling scheme is inadequate to determine any real interaction. Basic pharmacokinetic parameters such as clearance and volume are at best approximate values. There is a good deal of uncertainty in the estimation of half-life of bevacizumab therefore, half-life of this drug should be interpreted with great caution in the patient population. At this time the conclusions drawn by the Sponsor for drug-interaction studies are not acceptable from pharmacokinetics point of view.

/S/ 1/6/2005

Iftekhar Mahmood, Ph.D.
Clinical Pharmacology Reviewer

/S/ 1/14/04

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2 pages redacted from this section of the approval package consisted of draft labeling

Study #1

Title: A phase I, open-label, multicenter, dose-escalation study of the initial safety and pharmacokinetic profiles of recombinant humanized anti-VEGF monoclonal antibody (rhuMab VEGF) in subjects with advanced malignancies (study # —

This was a Phase I, open-label, dose-escalation pharmacokinetic (PK) study of rhuMab VEGF without concomitant therapy. There were three phases of the study: a screening period, a treatment period (study days 0-42), and a follow-up period (days 43-72). Five doses of rhuMab VEGF (0.1, 0.3, 1.0, 3.0, and 10 mg/kg) were evaluated in this trial and five subjects were enrolled at each dose level. At each dose level, dosing began with a single IV infusion of rhuMAb VEGF on day 0 for that cohort. Following the initial administration, subjects were monitored for safety for 28 days. Subjects who tolerated the initial dose of rhuMab VEGF received the same dose on Days 28, 35, and 42. Subjects aged ≥18 years with a histologically confirmed advanced solid malignant tumor for which no curative therapy existed or that had progressed despite treatment (measurable or evaluable disease) were eligible for study participation. Overall, there were 25 subjects in the study (8 males and 17 females; age ranged from 21 to 70 years). The subjects received rhuMab VEGF as a continuous IV infusion over 90 minutes. Blood samples were collected for 28 days following administration of the first dose, for 8 hours after each dose on days 28 and 35, and for 30 days after administration of the last dose on day 42. Serum rhuMab VEGF concentrations were measured using an enzyme-linked immunosorbent assay (ELISA), utilizing truncated rhVEGF and —

— Limit of detection was — ng/mL. Serum VEGF concentrations were measured by an ELISA using the — antibody (lower limit of detection = — pg/mL).

Pharmacokinetic parameters were estimated using a one- or two-compartment model. Table 1.1 summarizes the PK parameters of rhuMab VEGF administered to patients following IV infusion. The clearance of rhuMab VEGF appears to decrease with increasing dose. Volume of distribution of the central compartment (Vc) and at steady state ranged from 37.9 to 48.0 mL/kg and 50.1 to 60.4 mL/kg, respectively. Both volumes were independent of the dose given to the patients. The half-life of rhuMab

VEGF was approximately 14 to 15 days by the compartmental analysis. A non-compartmental analysis indicated that half-life after single and multiple dose ranged from 13 to 20 days (Table 1.2). Following multiple dosing no accumulation of drug was noted and the PK of rhuMab VEGF was similar following single and multiple dosing (Table 1.3).

TABLE 1.1

Selected Compartmental Pharmacokinetic Parameters following IV Infusion of Bevacizumab in Study — (Mean ± SD)

Dose (mg/kg)	n	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)	$t_{1/2}$ initial [a] (days)	$t_{1/2}$ terminal [b] (days)	MRT (days)
0.1	5	9.29±7.07	48.0±17.4	50.1±17.0	NA	5.21±2.41	7.40±3.44
0.3	5	5.07±2.39	48.6±13.0	60.3±7.30	1.9	10.4±5.34	13.9±6.11
1.0	5	3.27±0.81	37.9±7.77	60.4±18.8	1.30±0.535	14.7±6.92	19.9±9.25
3.0	4	3.65±2.10	41.4±12.0	53.4±12.0	0.844	12.8±6.60	18.1±9.36
10	5	2.75±0.47	43.5±12.6	53.0±10.9	2.17	14.2±3.36	19.3±3.18

TABLE 1.2

Terminal Half-Life Estimates in Study — by Non-Compartmental Methods (Mean ± SD)

Dose (mg/kg)	Terminal Half-Life (days)		
	First Dose (n)	Fourth Dose (n)	Mean of First and Fourth Doses (n)
1	12.5±4.05 (5)	14.4±5.56 (5)	13.4±4.69 (10)
3	18.1±6.49 (5)	19.4±11.3 (4)	18.7±8.33 (9)
10	14.3±2.45 (5)	20.2±8.37 (5)	17.3±6.59 (10)

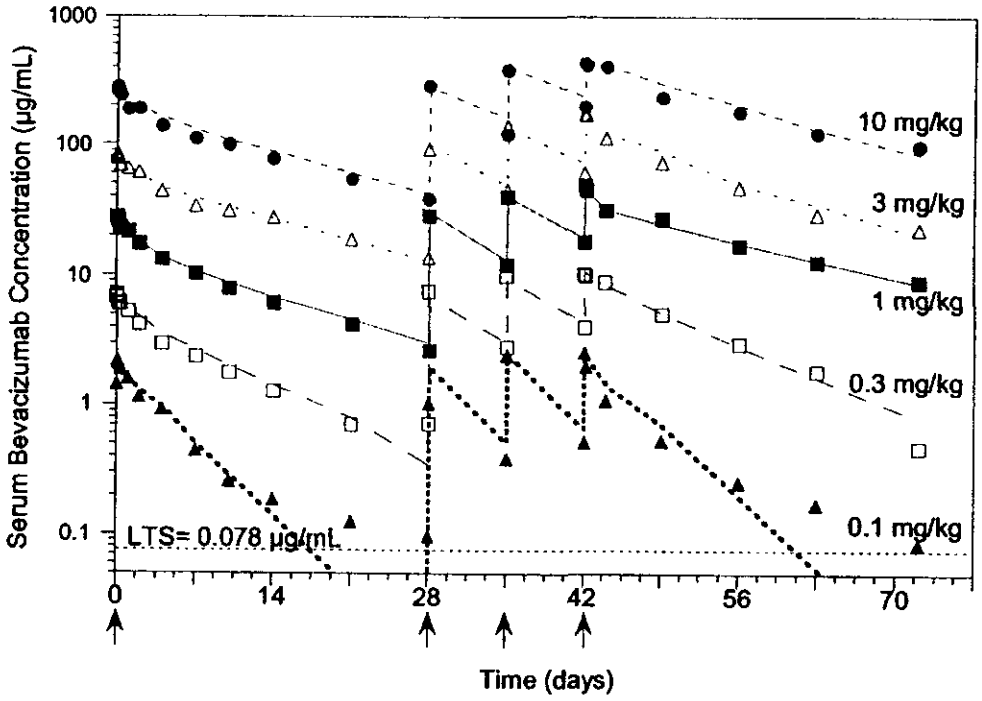
TABLE 1.3

Bevacizumab Pharmacokinetic Parameters Estimated Using First-Dose Data and All Available Data in Study — (Mean ± SD)

Dose (mg/kg)	n	CL (mL/day/kg)		V_c (mL/kg)	
		First Dose	All Data	First Dose	All Data
0.1	5	9.13±6.90	9.29±7.07	44.9±16.5	48.0±17.4
0.3	5	5.50±2.47	5.07±2.39	47.1±11.5	48.6±13.0
1.0	5	3.55±0.716	3.27±0.811	37.8±8.85	37.9±7.77
3.0	4	3.45±1.82	3.65±2.10	40.6±11.4	41.4±12.0
10	5	2.81±1.14	2.75±0.472	41.1±9.19	43.5±12.5

FIGURE 1.1

Mean Bevacizumab Concentration–Time Profiles in Study —



When comparing the parameters estimated using all available data with those estimated after the first dose, the CL estimates were 2.9% higher and the Vc estimates were 3.2% lower using the single-dose data. These results demonstrate that the pharmacokinetics of bevacizumab are similar when administered as a single dose or when administered as a total of four doses.

In conclusion, the pharmacokinetics of bevacizumab were characterized by higher clearance at doses of <1 mg/kg, and Vc did not change with increasing doses. Bevacizumab clearance was slow, with mean terminal half-life values ranging from 13 to 15 days by compartmental methods and 13 to 19 days by non-compartmental methods. Bevacizumab disposition was also similar when administered either as a single dose or as multiple doses. The Sponsor's comparison however, is not appropriate. The

Sponsor should have compared the PK data after the first dose and the last dose, rather than comparing the first dose with the all four doses.

Serum VEGF concentrations

Serum VEGF concentrations were measured on days 0, 1, 7, 29, 35, 42, 49, and 72. Prior to rhuMAb VEGF administration, individual serum VEGF concentrations ranged from — pg/mL to — pg/mL. An increase in serum total VEGF concentration was observed across all dose groups; the increase was more consistent with doses of >1.0 mg/kg. The mean AUC $_{(0\text{-}t)}$ was 3.54×10^3 and 5.13×10^3 pg/mL/day for the 0.1 and 0.3 mg/kg dose, respectively. When rhuMAb VEGF doses of ≥1.0 mg/kg were administered, serum VEGF concentrations increased over time in most subjects. The AUC $_{(0\text{-}t)}$ was 1.44×10^4, 1.21×10^4, and 2.59×10^4 pg/mL/day for the 1.0, 3.0, and 10 mg/kg dose, respectively. At the three highest doses, maximum concentrations were reached after the day 42 rhuMAb VEGF administration in most subjects, and concentrations did not return to baseline levels by day 72 in most subjects. There was no relationship between baseline serum VEGF concentrations and rhuMab VEGF clearance. Table 1.4 is the summary of serum VEGF AUC as the function of rhuMab VEGF dose. Serum VEGF concentrations increased with increasing dose.

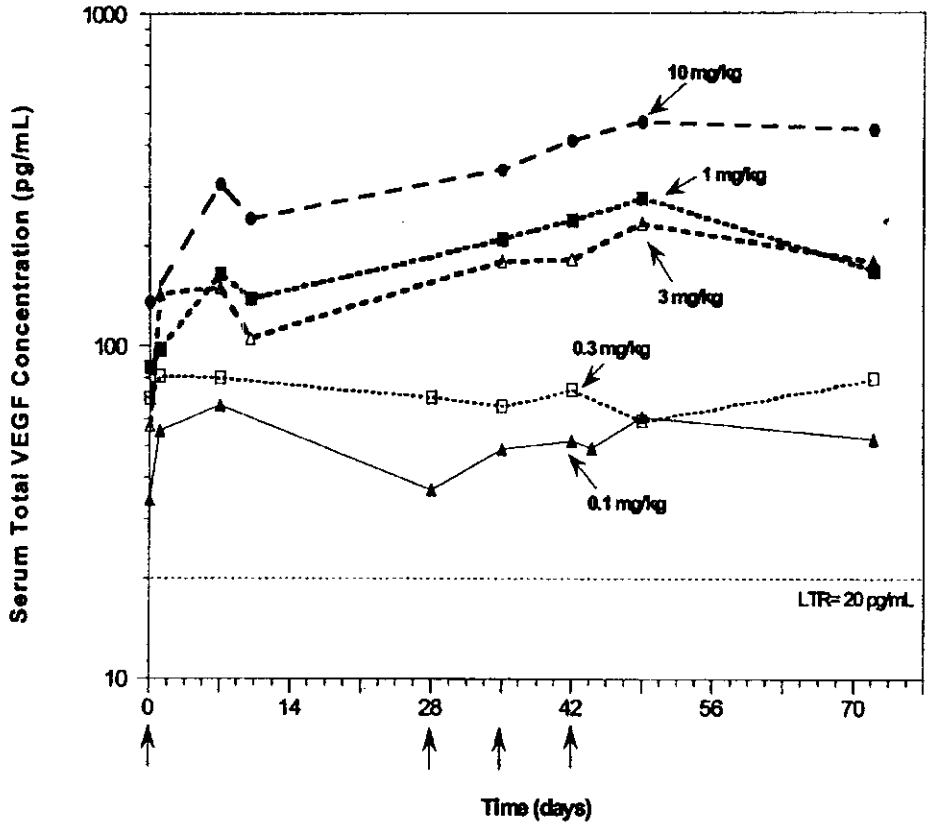
TABLE 1.4

Serum VEGF AUC as the function of rhuMab VEGF dose

Dose (mg/kg)	AUC (pg/mL/day)
0.1	3540
0.3	5130
1.0	14400
3.0	12100
10.0	25900

FIGURE 1.2

Mean Serum VEGF Concentration–Time Profiles



Arrow = indicate days of rhuMAb VEGF administration.

Conclusion:

After four doses of rhuMab VEGF, no accumulation of drug was noted in this study. This is because multiple doses were not given long enough to detect any accumulation of bevacizumab in the systemic circulation. It is anticipated that following multiple administration of rhuMab VEGF every 2 or 3 weeks some accumulation of drug may be observed. The accumulation of bevacizumab in Phase II studies (— and AVF0780g) was noted. The trough serum concentrations of bevacizumab following multiple doses of every 2 or 3 weeks after 1 year follow up indicated slightly over 2-fold increase in the trough concentrations as compared to the first dose.

Study #2

Title: A phase I, open-label, multicenter, dose-escalation study of the safety and pharmacokinetics of multiple doses of recombinant humanized monoclonal anti-VEGF antibody (rhuMab VEGF) in combination with chemotherapy in subjects with advanced solid malignancies (study # . —

This was a phase I, open-label, dose-escalation pharmacokinetic (PK) study of multiple IV doses of rhuMab VEGF to patients with a variety of advanced solid malignant tumors who were eligible for chemotherapy with either doxorubicin or carboplatin/paclitaxel or 5 –fluorouracil (5-FU)/leucovorin. There were three phases of the study: a screening period, a treatment period (study days 0-49), and a follow-up period (days 50-79). — of rhuMAb VEGF (— were supposed to be evaluated in this trial with a minimum of — subjects at each dose level (Table 2.1).

TABLE 2.1

Planned Study Design

rhuMAb VEGF Dose Level	Number of Subjects		
	Doxorubicin	Carboplatin/ Paclitaxel	5-FU/Leucovorin
— mg/kg		—	
— mg/kg		—	

However, due to drug shortage, —mg/kg rhuMAb VEGF was not given to the patients. A total of 8 doses of rhuMAb VEGF (over a 49-day period) were administered weekly to each subjects. During this same period, subjects also received at least one cycle (5-FU/leucovorin) or at least two cycles (doxorubicin or carboplatin/paclitaxel) of chemotherapy.

The average age of subjects enrolled in the trial was 48 years (range: 27-69 years). Six of 12 subjects (50%) were male and 11 of 12 (92%) were Caucasian. All 4 subjects in the carboplatin/paclitaxel group were male, whereas in the doxorubicin and 5-FU/leucovorin groups, 1 of 4 subjects (25%) was male. The types of cancers treated in

this study varied among the chemotherapy groups of the trial. In the doxorubicin group, 2 subjects had colorectal cancer, 1 subject had renal cell cancer, and 1 subject had sarcoma. In the carboplatin/paclitaxel group, 2 subjects had non-small cell lung cancer, 1 subject had leiomyosarcoma of the stomach, and 1 subject had carcinoid of the mediastinum and thymus. In the 5-FU/leucovorin group, 1 subject had breast cancer, 1 subject had colorectal cancer, 1 subject had a primitive neuroectodermal tumor, and 1 subject had cervical cancer. Table 2.2 summarizes the number of chemotherapy doses received by the patients.

TABLE 2.2

Cycles of Chemotherapy Received

Chemotherapy	Chemotherapy Doses	Number of Subjects
Doxorubicin	1	1 (25%)
	2	2 (50%)
	3	1 (25%)
Carboplatin/paclitaxel	2	3 (75%)
	3	1 (25%)
5-FU/leucovorin	6	4 [a] (100%)

[a] Chemotherapy treatment was delayed for 2 subjects.

Doxorubicin:

Doxorubicin was administered at a dose of 50 mg/m2 IV according to institutional standards on Days 0 (Cycle 1) and 28 (Cycle 2) for the two cycles within this study.

Carboplatin/Paclitaxel:

Carboplatin and paclitaxel were given in combination. Paclitaxel was administered after rhuMAb VEGF and before carboplatin. Paclitaxel was dosed at 175 mg/m^2 IV over 3 hours on Days 0 and 28. Carboplatin dosing was based on the Calvert Formula: Total dose (mg) = (Target AUC) x (GFR + 25), where GFR is the glomerular filtration rate in mL/min and the target AUC was 6 mg*min/mL.

5-FU/Leucovorin:

One cycle of 5-FU was to be dosed at 500 mg/m^2/week and administered for at least the first 6 of the 7 weeks of rhuMAb VEGF treatment. Leucovorin was dosed at 20 mg/m2/week on the same schedule as 5-FU.

Blood samples for determination of serum rhuMAb VEGF concentrations were collected at day 0 (predose, 10 minutes and 2 and 8 hours post-infusion) and on days 7, 14, 21, 28, 35, 42, and 49 (predose, 10 minutes post- infusion, i.e., trough and peak levels) and for 30 days after the administration of the last dose given on day 49. Blood samples were also collected for antibody to rhuMAb VEGF (predose on day 0) and for serum VEGF (predose on Days 0, 7, 14, 21, 28, 35, 42, and 49).

Blood samples for doxorubicin were collected prior to the doxorubicin dose, immediately (within 5 minutes) following completion of the doxorubicin dose, and 2 and 8 hours after completion of the doxorubicin dose on Days 0 and 28. Blood samples were collected for carboplatin, prior to the carboplatin dose, immediately (within 5 minutes) following completion of the carboplatin dose, 3 and 24 hours after completion of the carboplatin dose on Days 0 and 28. Blood samples were collected for paclitaxel prior to the paclitaxel dose, immediately (within 5 minutes) following completion of the paclitaxel dose, 3 and 24 hours after completion of the paclitaxel dose on Days 0 and 28. For 5-FU/leucovorin, blood samples were collected on days 0 and 35 only (5, 30, and 60 minutes after drug administration).

Serum rhuMab VEGF concentrations were measured using an enzyme-linked immunosorbent assay (ELISA), utilizing —

— Limit of detection was — ng/mL. Serum VEGF concentrations were measured by an ELISA using the — antibody (lower limit of detection = — pg/mL). Plasma 5-FU (lower limit of detection = — pg/mL) and paclitaxel (lower limit of detection = — ng/mL) concentrations were measured using a validated HPLC method with UV absorbance detection. Plasma platinum concentrations (lower limit of detection = — pg/mL) were measured by a validated — Plasma doxorubicin concentrations (lower limit of detection = — ng/mL) were determined by a validated HPLC method with fluorescence detection. Mean pharmacokinetic parameters of

rhuMab VEGF given with chemotherapy drugs and the PK parameters of chemotherapy drugs are summarized in Tables 2.1 and 2.2, respectively. Mean ± sd serum rhuMab concentration-time profiles are shown in Figure 2.1.

TABLE 2.1

Pharmacokinetic Parameters following IV Infusion of rhuMAb VEGF

Group (n)	C_{max} (µg/mL) Day 0	C_{max} (µg/mL) Day 49	CL (mL/day/kg)	V_c (mL/kg)	$t_{1/2}$ terminal (days)	MRT (days)
Doxorubicin (3)	59.4± 11.81	144.7±18.18	3.74±0.555	64.8±8.68	12.1±0.603	17.40±0.854
Carboplatin/ paclitaxel (4)	80.9± 30.05	185.4±61.65	2.48±0.436	51.7± 14.03	14.23±1.55	20.55±2.263
5-FU/ leucovorin (4)	65.8± 25.91	162.0±43.84	3.28±0.857	56.0± 12.25	12.51±4.39	18.1±6.355
All groups (11)	69.5± 24.26	166.6±45.94	3.11±0.792	56.8± 12.21	13.01±2.754	18.78±3.979

Figure 2.1

Mean Serum rhuMAb VEGF Concentration–Time Profiles

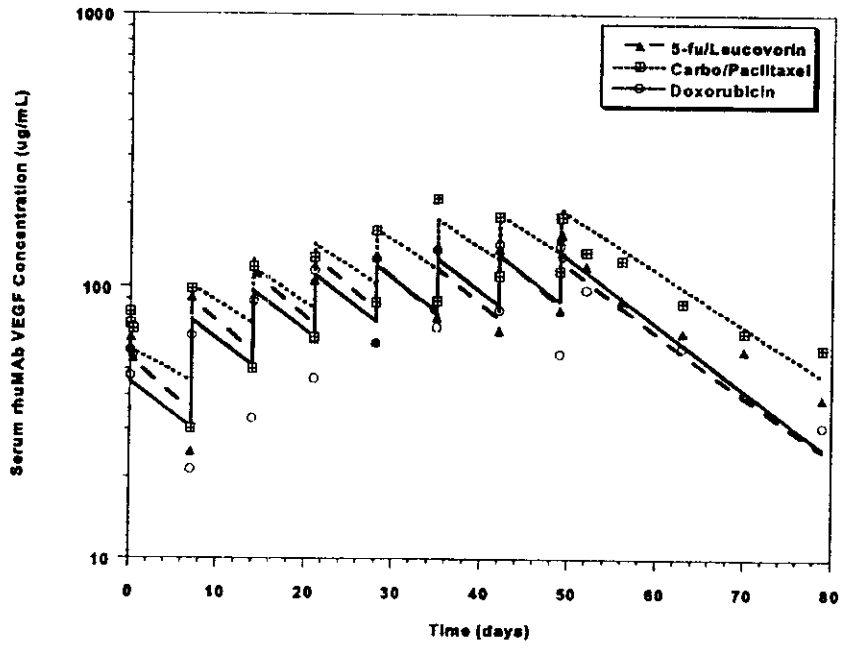


TABLE 2.2

Mean Plasma Concentrations of Chemotherapy Drugs (Mean±SD)

	Timepoint					
	First Dose			Day 28		
Chemotherapy	5 min	2 hr	8 hr	5 min	2 hr	8 hr
Doxorubicin (ng/mL)	1280 ±411	40.0 ±12.2	32.1 ±13.8	942 ±1065	48.5 ±10.5	21.4 ±3.32

	Timepoint					
	First Dose			Day 28		
Chemotherapy	5 min	3 hr	24 hr	5 min	3 hr	24 hr
Carboplatin (µg/mL)	48.3 ±15.2	12.0 ±0.816	1.83 ±0.126	29.3 ±10.2	11.0 ±0.816	1.93 ±0.222
Paclitaxel (ng/mL)	2933 ±549	547 ±117	71.4 ±11.0	2740 ±901	458 ±118	53.9 ±13.6

	Timepoint					
	First Dose			Day 35		
Chemotherapy	5 min	30 min	1 hr	5 min	30 min	1 hr
5-FU (µg/mL)	24.9 ±15.9	3.80 ±4.80	0.529 ±0.610	18.4 ±11.2	4.25 ±4.31	0.377 ±0.411

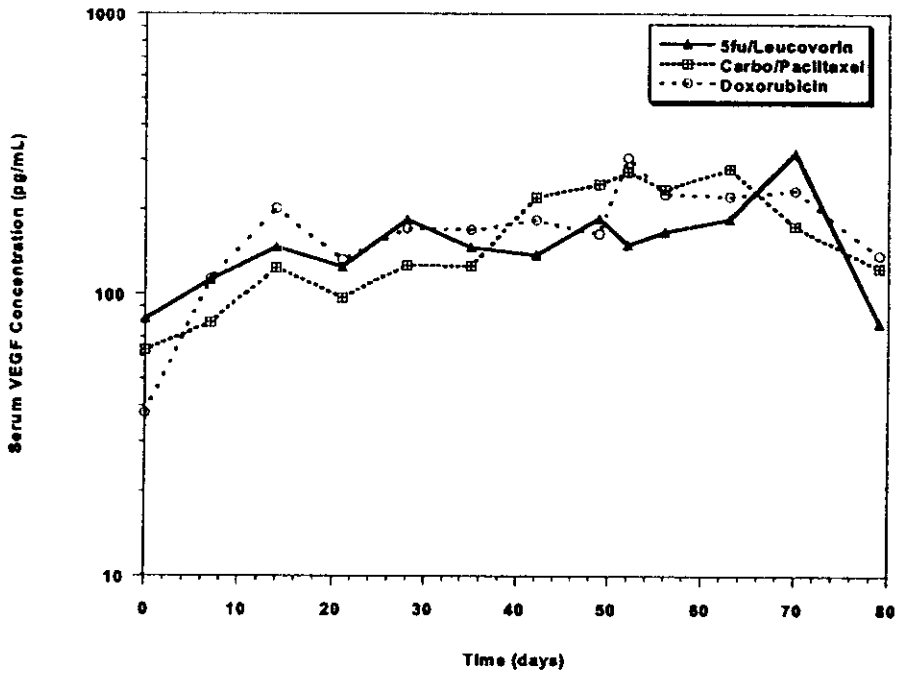
Following concomitant, multiple-dose administration of rhuMAb VEGF in combination with either doxorubicin, or carboplatin/paclitaxel, or 5-FU/leucovorin, rhuMAb VEGF disposition was characterized by a low clearance and a low volume of distribution. Although the mean rhuMAb VEGF clearance was lower in the carboplatin/paclitaxel group than the other two groups, it was consistent with that estimated in a previous study (AVF0737g), in which the mean clearance ranged from 2.65 to 3.75 mL/day/kg with rhuMAb VEGF doses ranging from 1.0 mg/kg to 10 mg/kg. The increase in total serum VEGF concentrations over time was also consistent with the results of the previous study. Multiple dosing of rhuMab VEGF appears to decrease the concentrations of chemotherapy drugs on day 28 compared to the first dose. This decrease however, is very small and clinically may be insignificant.

Serum-VEGF concentrations:

Individual baseline serum VEGF concentrations ranged from —— pg/mL, with an overall mean (when combining subjects from all three groups) of 66.9 ± 40.6 pg/mL. Following rhuMAb VEGF administration, VEGF serum concentrations increased over time in most subjects. Cmax ranged from —— pg/mL, with mean values ranging from 272 to 351 pg/mL for the doxorubicin and 5-FU/leucovorin groups, respectively. T max ranged from 7 to 70 days, with mean values of 39 days for the 5-FU/leucovorin and 57 days for the two other groups. Individual $AUC_{(0-t)}$ values ranged from —— day.pg/mL with mean values ranging from 11,200 to 13,600 day.pg/mL for the 5-FU/leucovorin and doxorubicin groups, respectively. Serum VEGF concentrations had not returned to baseline by Day 79 in most subjects.

Figure 2.2

Mean Serum VEGF Concentration–Time Profiles



Conclusion: Due to very small sample size and blood sampling scheme it is very difficult to make any definite conclusion about the impact of chemotherapy drugs on the pharmacokinetics of rhuMab VEGF or vice versa.

Study #3

Title: A pilot phase II, open-label, multidose study to evaluate the efficacy, safety, and pharmacokinetics of recombinant humanized monoclonal anti-VEGF (rhuMab VEGF) in subjects with — (study # —) .

In this phase II study, 15 subjects with — (age ranged from 62 to 83 years) received 10 mg/kg bevacizumab (IV infusion for 90 minutes) every two weeks till day 70. The study was terminated after the first cohort of 15 subjects was treated with 10 mg/kg bevacizumab due to the lack of response. Blood samples were collected on day 0 and at 10 minutes, 2 hours, and 6 hours post-infusion and on days 14, 28, 42, 56, 70, 98, 126, 154, and 182 (predose and 10 minutes post-infusion). Serum rhuMab VEGF concentrations were measured using an enzyme-linked immunosorbent assay (ELISA), utilizing — — Limit of detection was — ng/mL. Serum VEGF concentrations were measured by an ELISA using the . — antibody (lower limit of detection = — pg/mL).

Following the first dose, mean peak concentrations of rhuMAb VEGF were 247 ng/mL and mean trough concentrations were 67 ng/mL. Following multiple dosing peak and trough concentrations increased over time. At day 98, mean peak concentrations were 450 ng/mL and mean trough concentrations were 180 ng/mL. Individual estimates of CL ranged from — mL/day/kg, with a mean value of 2.71 mL/day/kg. Individual values of Vc ranged from . — mL/kg, with a mean value of 46.1 mL/kg. Individual estimates of t1/2 ranged from 7.5 to 22 days, with a mean value of 13 days. The following Table summarizes the PK parameters (mean ± sd) of rhuMab VEGF.

TABLE 3.1

Mean Serum rhuMAb VEGF Pharmacokinetic Parameters

Dose Group (mg/kg) (N)	CL (mL/day/kg)	V_c (mL/kg)	$t_{1/2}$ (days)	MRT (days)
10 (15)	2.71±0.745	46.1±5.54	12.7±3.93	18.3±5.67

Prior to rhuMAb VEGF administration, serum VEGF concentrations were less than 20 pg/mL in 8 of the 15 subjects. In subjects in whom VEGF was quantifiable, the baseline serum VEGF concentrations ranged from 24 to 178 pg/mL. Following rhuMAb VEGF administration, serum VEGF concentrations increased over time in all subjects. C_{max} ranged from —— pg/mL, with a mean value of 590 pg/mL. T max ranged from 29 to186 days, but since subjects discontinued the study at various times, Tmax was not well estimated. Individual AUC_{last} values ranged from —— day*pg/mL, with a mean value of 54,000 day*pg/mL. By the last sampling time point (which varied with each subject), C_{last} remained higher than C_0. The following Table is the summary of VEGF pharmacokinetic parameters (mean $\pm$ sd).

TABLE 3.2

Mean Serum VEGF Pharmacokinetic Parameters

Dose Group (mg/kg) (N)	C_0 (pg/mL)	C_{max} (pg/mL)	T_{max} (day)	AUC_{0-t} (day•pg/mL)	C_{max}/C_0
10 (15)	67.8±60.2	590±301	110±55.6	54000±31400	22.0±16.8

The pharmacokinetic results obtained in this study confirmed the observations noted in the previous studies (Studies 1 & 2).

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Study #4

Title: A phase II, multidose, randomized, multicenter clinical trial to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of recombinant humanized monoclonal anti-VEGF antibody (rhuMab VEGF) combined with carboplatin and paclitaxel chemotherapy in subjects with locally advanced or metastatic (stage IIIB or IV) non-small cell lung cancer (study # —).

This Phase II, randomized, open-label, multicenter clinical trial was designed to evaluate the efficacy and safety of rhuMAb VEGF when combined with paclitaxel/carboplatin chemotherapy in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC). Patients with Stage IIIb (with pleural effusion), Stage IV, or recurrent NSCLC were eligible for enrollment. There were three phases of the study: a 28-day screening period, a treatment period lasting up to 357 days, and a 21-day follow-up period. Following enrollment, subjects were randomized to one of three treatment arms: one control arm and two rhuMAb VEGF treatment arms. Randomization was stratified by ECOG performance status (ECOG status of 0 or 1 vs. 2). All subjects were to receive up to six cycles of paclitaxel/carboplatin chemotherapy. Subjects randomized to the rhuMAb VEGF treatment arms received either 7.5 mg/kg or 15 mg/kg rhuMAb VEGF every 3 weeks in addition to paclitaxel/carboplatin. Subjects received paclitaxel/carboplatin chemotherapy on the first day of each 3-week cycle for up to six cycles. For those subjects randomized to a rhuMAb VEGF treatment arm, rhuMAb VEGF was administered every 3 weeks (on the same day as chemotherapy administration) until evidence of disease progression, or for a total of 1 year (357 days) of continuous rhuMAb VEGF therapy, whichever occurred first. RhuMab VEGF was administered to patients as a 90-minute IV infusion. Chemotherapy administration was to be completed at least 1 hour before rhuMab VEGF infusion. Paclitaxel/carboplatin were given sequentially, with paclitaxel given first. Paclitaxel was dosed at 200 mg/m^2 IV over 3 hours. Carboplatin dosing began within 60 minutes after completion of paclitaxel infusion and was based on the Calvert Formula:
Total dose (mg) = (Target AUC) x (GFR + 25), where GFR is the glomerular filtration rate in mL/min and the target AUC was 6 mg*min/mL.

Blood samples for determination of serum rhuMAb VEGF concentrations were collected at pre-dose, 10 minutes and 2 hours post-dose after the first infusion and at pre-dose and 10 minutes post-dose upon all subsequent rhuMab VEGF infusions. Blood samples were also collected for antibody to rhuMAb VEGF prior to chemotherapy administration on day 0 in subjects randomized to rhuMab VEGF plus chemotherapy; prior to rhuMab VEGF administration in subjects who crossed over to rhuMab VEGF monotherapy. Blood samples for paclitaxel were drawn in cycles 1 and 4, pre-dose, immediately (i.e., within 5 minutes) following completion of paclitaxel infusion and 3 hours after completion of the infusion. Samples were collected in a total of 24 subjects: 12 from the control arm and 12 from the15 mg/kg rhuMAb VEGF arm. Blood samples for carboplatin were also drawn in Cycles 1 and 4, pre-dose, immediately (within 5 minutes) following completion of carboplatin infusion and 3 hours after completion of the infusion. Samples were collected in a total of 24 subjects: 12 from the control arm and 12 from the15 mg/kg rhuMAb VEGF arm.

Serum rhuMab VEGF concentrations were measured using an enzyme-linked immunosorbent assay (ELISA), utilizing ——— ——— Limit of detection was — ng/mL. Serum VEGF concentrations were measured by an ELISA using the — antibody (lower limit of detection = — pg/mL). Paclitaxel (lower limit of detection = — ng/mL) concentrations were measured using a validated HPLC method ——— — Plasma platinum concentrations (lower limit of detection = — ng/mL) were measured by ———

A total of 67 subjects were randomized to one of the two rhuMab VEGF arms. Of the 67 subjects subjects randomized, 66 received at least one dose of rhuMab VEGF and 62 subjects had serum concentrations to perform one compartment PK analysis. Serum rhuMAb VEGF concentrations appeared to plateau by day 105. On day 105, peak concentrations were 267 $\pm$ 55 and 601 $\pm$ 160 ng/mL, and trough levels were 73 $\pm$ 43 and 135 $\pm$ 48 ng/mL for the 7.5 and 15 mg/kg doses, respectively. Pharmacokinetic parameters are summarized in Table 4.1.

TABLE 4.1

Serum rhuMAb VEGF Pharmacokinetic Parameters following rhuMAb VEGF Administration (Arithmetic Mean ± Standard Deviation)

Arm	AUC_{inf} (µg/mL·day)	CL (mL/kg/day)	Vol (mL/kg)	$t_{1/2}$ (day)	MRT (day)
7.5 mg/kg (n=30)	2950±1085	2.98±1.39	42.9±9.1	11.2±3.55	16.2±5.12
15 mg/kg (n=32)	6162±1897	2.75±1.16	39.4±8.69	10.7±2.64	15.5±3.81

There was no difference in clearance or volume of distribution between the two rhuMAb VEGF arms. A gender difference was observed in clearance, with a mean clearance of 2.40 ± 1.17 mL/kg/day in women and 3.24 ± 1.25 mL/kg/day in men ($p<0.01$). Age had no impact on the clearance or volume of distribution of rhuMab VEGF.

The effect of tumor burden on rhuMAb VEGF clearance was also evaluated. Tumor burden was defined as the sum of the areas of all measurable lesions (cm^2). Clearance was faster in subjects with a tumor burden above the median (25.28 cm^2); mean clearance was 3.30 ± 1.52 and 2.47 ± 0.85 mL/kg/day for subjects with tumor burden above and below the median, respectively ($p<0.02$).

RhuMAb VEGF clearance was lower in subjects with an Eastern Cooperative Oncology Group (ECOG) status of 0 ($p<0.01$), with mean values of 2.43 ± 1.11 and 3.35 ± 1.29 mL/kg/day for subjects with an ECOG status of 0 and ≥1, respectively.

When pharmacokinetic parameters were compared between subjects with a serum albumin concentration above and below the median of 3.5 g/dL (the lower limit of the normal range [— g/dL]), clearance was higher in subjects with baseline serum albumin levels of <3.5 g/dL ($p<0.01$) compared with a baseline albumin concentration of ≥3.5 g/dL, with mean values of 3.31 ± 1.31 and 2.35 ± 1.02 mL/kg/day, respectively.

Plasma VEGF Pharmacokinetics:

At baseline, plasma samples for 4 of 78 subjects were above the assay limit of quantification of — pg/mL. The VEGF levels of the remaining 74 subjects were below the detectable limit. An increase in total plasma VEGF concentration was observed in both rhuMAb VEGF arms, with average maximum concentrations of 130 ± 87.3 and

325 ± 215 pg/mL for the 7.5 and 15 mg/kg arms, respectively. This corresponds to an average 3- and 7 -fold increase in plasma VEGF levels over baseline for the 7.5 and 15 mg/kg dose, respectively. The pharmacokinetic parameters (mean ± sd) of plasma VEGF are summarized in Table 4.2.

Table 4.2

Plasma VEGF pharmacokinetic parameters following rhuMab VEGF administration

Arm	C_{max} (pg/mL)	C_{max}/C_0	$AUC_{0\text{-}Tlast}/T_{last}$ (pg/mL)
Control	51.9±37.1 n=20	1.24±0.981 n=17	43.8±13.6 n=20
7.5 mg/kg	130±87.3 n=25	3.13±2.28 n=21	81.0±44.1 n=25
15 mg/kg	325±215 n=31	7.34±4.22 n=26	198±114 n=31

Carboplatin and paclitaxel pharmacokinetics:

In the control arm, plasma concentration data from both Day 0 and Day 63 were available for 6 subjects for paclitaxel and 6 subjects for carboplatin. In the 15 mg/kg arm, data were available for 8 subjects for paclitaxel and 9 subjects for carboplatin. Table 4.3 describes the ratio of $AUC_{(0\text{-}180)}$ min from Cycles 1 to 4. Based on this limited sample size, there did not appear to be a difference in the disposition of either paclitaxel or carboplatin when each was administered alone or in combination with rhuMAb VEGF. However, it should be noted that while the paclitaxel concentrations in the control arm at Day 63 were all greater than the concentrations at Day 0, 3 of the 8 subjects in the 15 mg/kg arm had concentrations at Day 63 that were substantially lower than those at Day 0.

TABLE 4.3

Ratio of Chemotherapy Exposure after Four Cycles of Carboplatin and Paclitaxel

Arm	Carboplatin	Paclitaxel
Control		
n	6	6
Mean	1.012±0.142	1.24±0.178
Range	[illegible]	
15 mg/kg		
n	9	8
Mean	1.047±0.210	1.105±0.537
Range	[illegible]	

Values are mean ± sd.

RhuMAb VEGF Concentration-Effect Relationship:

The relationship between rhuMAb VEGF pharmacokinetic parameters and time to disease progression was also evaluated. The relationship between AUC_{inf} and time to disease progression (IRF [cavitation]/investigator assessment) was evaluated by dividing the AUC_{inf} into quartiles (AUC_{inf} <2875, AUC_{inf} =2875-4050, AUC_{inf} =4050-6075, and AUC_{inf} >6075 mcg/mL*day). In subjects with an AUC_{inf} greater than the median of 4050 mcg/mL*day, the median time to disease progression was 293 days (203-373 days), whereas in subjects with an AUC_{inf} less than the median AUC_{inf}, the median time to disease progression was 84 days (57-201 days). An AUC_{inf} of >4050 mcg/mL*day was observed in 27 of 32 subjects (84.4%) in the 15 mg/kg arm. The strong association of baseline albumin with both clearance and time to disease progression suggests that drug exposure may be related to health status; therefore, the relationship between pharmacokinetic parameters and time to disease progression should be interpreted with caution. Table 4.4 shows the association of pharmacokinetic parameters with the combined IRF (cavitation)/investigator assessments of time to disease progression.

TABLE 4.4

Log-Rank Test of the Association of Pharmacokinetic Parameters with Time to Disease Progression (IRF [Cavitation]/Investigator Assessment)

Variable	Strata	Median Time to Progression (days)	p-value
AUC_{inf}	>4050 µg/mL•day	293.0	0.0059
	≤4050 µg/mL•day	84.0	
CL	>2.56 mL/kg/day	92.0	0.0018
	≤2.56 mL/kg/day	219.0	
C_{max}	>270 µg/mL	233.0	0.1721
	≤270 µg/mL	171.0	
k_{10}	>0.0629 /day	152.0	0.2804
	≤0.0629 /day	207.0	
Vol	>39.3 mL/kg	171.0	0.0459
	≤39.3 mL/kg	213.0	

Conclusion:

The increase in the AUC of rhuMab VEGF is dose proportional. The half-life of rhuMab VEGF is shorter in this study as compared to the previous studies. There appears to be a relationship between AUC of rhuMab VEGF and median time to progression when rhuMab VEGF was given with carboplatin and paclitaxel.

Study #5

Title: A phase II, multidose, randomized, multicenter clinical trial to evaluate the efficacy, safety, and pharmacokinetics of recombinant humanized monoclonal anti-VEGF antibody (rhuMab VEGF) combined with 5-fluorouracil and leucovorin chemotherapy in subjects with metastatic colorectal cancer (study # AVF0780g).

This Phase II, randomized, open-label, multicenter clinical trial was designed to evaluate the efficacy and safety of rhuMAb VEGF when combined with 5-fluorouracil and leucovorin in subjects with metastatic colorectal cancer. One hundred four subjects with metastatic colorectal carcinoma were randomized to one of three treatment arms: one control arm (5-FU/leucovorin chemotherapy alone) and two arms of bevacizumab treatment (5 or 10 mg/kg every 2 weeks + 5-FU/leucovorin). 5-FU/leucovorin chemotherapy was administered weekly for the first 6 weeks of an 8-week cycle; subjects received at least one cycle of chemotherapy. 5-FU/leucovorin chemotherapy was continued until evidence of progressive disease. Bevacizumab was administered every 2 weeks until evidence of disease progression or for up to a total of 24 doses, whichever occurred first. Blood samples for determination of rhuMab VEGF were collected at predose, 10 minutes and 2 hours after completion of the first bevacizumab infusion, and predose and10 minutes after completion of all subsequent infusions. Serum bevacizumab pharmacokinetics were characterized by a one-compartmental model. The patients received 500 mg/m^2 IV leucovorin infusion for 2 hours, once weekly for the first 6 weeks of each cycle and 500 mg/m^2 IV 5-FU by slow bolus push, 1 hour after initiation of the leucovorin administration. A sparse sampling scheme was used to measure plasma 5-FU concentrations in 19 subjects enrolled in the 10 mg/kg group. The concentrations measured at 0, 10 minutes, and 2 hours after 5-FU administration on Day 0 (before bevacizumab dosing) were compared with those measured on Day 35 (after three bevacizumab doses). VEGF concentrations increased following rhuMAb VEGF administration. There was no relationship between time to disease progression or survival and any of the exposure parameters. Although the data were variable, there were no systematic changes in 5-FU concentrations between day 0 and day 35. The pharmacokinetic parameters (mean $\pm$ sd) of bevacizumab are summarized in Table 5.1.

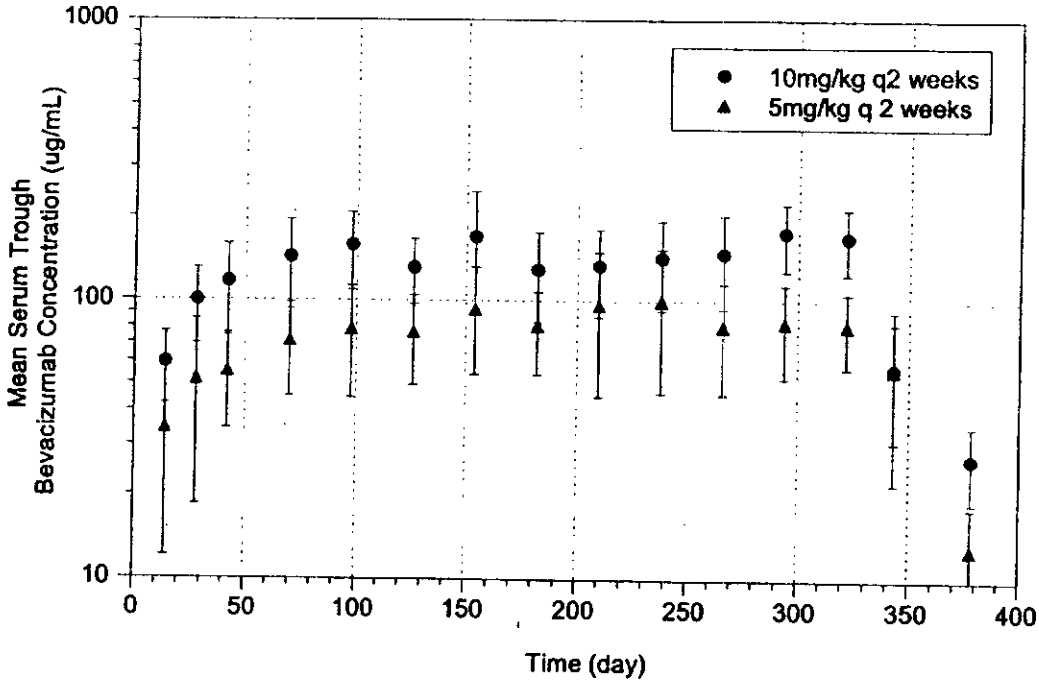
TABLE 5.1

Mean rhuMAb VEGF Pharmacokinetic Parameters

Arm	n [a]	CL (mL/day/kg)	V_c (mL/kg)	$t_{1/2}$ (days)	MRT (days)	AUC_{inf} (µg•day/mL)
5 mg/kg	34	2.79 ± 0.849	45.4 ± 9.02	12.0 ± 3.22	17.3 ± 4.65	2009 ± 653
10 mg/kg	28	2.78 ± 0.663	46.1 ± 8.84	12.0 ± 3.47	17.4 ± 5.00	3810 ± 1002

FIGURE 5.1

Mean Trough Concentration–Time Profiles of Bevacizumab in Study AVF0780g



Conclusion:

From this study the Sponsor concludes that rhuMAb VEGF does not appear to have any effect on plasma 5-FU concentrations. Such an assessment may be incorrect due to insufficient blood sampling for 5-FU. Therefore, from this study it is difficult to assess if indeed rhuMab VEGF had no impact on the PK of 5-FU.

Study #6

Title: A phase II, open-label, multidose, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of recombinant humanized monoclonal anti-VEGF antibody (rhuMab VEGF) as monotherapy in subjects with relapsed metastatic breast cancer (study # —

Seventy-five subjects with metastatic breast cancer who had progressed following at least one anthracycline- and/or taxane-based chemotherapy, received bevacizumab as a single agent every 2 weeks for a total of six infusions. Cohorts of subjects were initially enrolled into the 3 mg/kg dose group. Due to lack of response, the subjects then received doses of 10 mg/kg and 20 mg/kg. Blood samples were drawn at time 0, every 30 minutes during bevacizumab infusion, and at 90 minutes following completion of the first infusion. Subsequently, samples were taken at time 0, every 30 minutes during bevacizumab infusion, and at 30 and 60 minutes following each bevacizumab infusion. PK parameters were estimated using a one-compartment model in 74 subjects. The pharmacokinetics of bevacizumab were linear across the doses. Table 6.1 summarizes the pharmacokinetic parameters of bevacizumab.

TABLE 6.1

Selected Pharmacokinetic Parameters following IV Infusion of Bevacizumab in Study — (Mean±SD)

Dose (mg/kg/2wk)	n	CL (mL/day/kg)	V_c (mL/kg)	MRT (days)
3	17	2.95±1.29	39.0±9.4	14.1±3.20
10	41	2.74±1.11	40.1±9.6	15.6±3.91
20	16	3.15±0.75	39.0±7.3	12.8±2.79

An increase in plasma VEGF concentrations was observed in all dose groups. A 4.6, 7.7, and 9.8 fold increase in VEGF concentrations over baseline for 3, 10, and 20 mg/kg dose group was noted. Overall, the results of this study are consistent with the findings of the previous studies.

Study #7

Title: A Multicenter, open-label, phase III, randomized, active-controlled trial evaluating the efficacy, safety, and pharmacokinetics of rhuMAb VEGF (Bevacizumab), in combination with capecitabine chemotherapy, in subjects with previously treated metastatic breast cancer (study # AVF2119g).

Four hundred sixty-two subjects were enrolled and randomized in a 1: 1 ratio to one of two treatment arms: one active-control arm (capecitabine alone) and one rhuMAb VEGF arm (15 mg/kg rhuMAb VEGF + capecitabine). RhuMAb VEGF was administered by intravenous (IV) infusion every 3 weeks for up to 35 cycles or until prohibitive rhuMAb VEGF-related toxicity occurred, whichever occurred first. Capecitabine was administered twice daily for 2 weeks followed by a 1-week rest period (3-week cycle) at a dose of either 2500 mg/m2 per day (creatinine clearance, >50 mL/min) or 1875 mg/m2 per day (creatinine clearance, 30-50 mL/min) rounded down to the nearest 500 mg. Capecitabine administration continued for a total of 35 cycles or until disease progression or prohibitive capecitabine-related toxicity, whichever occurred first. Blood samples were collected before and 10 minutes following completion of bevacizumab infusion on day 0 of cycles 1, 3, 5, 7, and 9 and at study completion or early termination. Serum bevacizumab concentration-time data were fitted to a one-compartment model. Plasma concentrations of capecitabine and its metabolites 5-FU and 5'-DFUR (5-deoxy-5-fluorouridine) were measured at 90, 150, and 240 minutes after capecitabine administration.

The clearance and volume of distribution (mean $\pm$ sd) of bevacizumab were 2.08 $\pm$ 0.51 mL/kg/day and 34.3 $\pm$ 7.6 mL/kg, respectively. Both these values are consistent with the previous studies. The PK parameters for capecitabine and its metabolites are summarized in Table 7.1.

TABLE 7.1

Dose-Adjusted AUC for Capecitabine and Its Metabolites: Cycle 1, Week 2 (Geometric Mean, Ratio, and 95% CI)

Group	Capecitabine (ng • day/mL)	5'-DFUR (ng • day/mL)	5-FU (ng • day/mL)
Capecitabine alone (n=19)	109	321	18.6
Bevacizumab + capecitabine (n=21)	70.1	237	15.0
Ratio (95% CI)	0.65 (0.39, 1.07)	0.74 (0.50, 1.08)	0.80 (0.53, 1.21)

From the results of this study it appears that bevacizumab does have an effect on capecitabine concentrations. Bevacizumab lowered the AUC of capecitabine by 36%. It is however, surprising that the AUC of 5'-DFUR is also lower when given with bevacizumab (traditionally the metabolite levels should go up with decreasing concentrations of the parent compound). The study design is not adequate enough to make a definite conclusion if indeed bevacizumab has any effect on the PK of capecitabine.

Study #8

Title: A phase III, multicenter, randomized, active-controlled clinical trial to evaluate the efficacy and safety of rhuMab VEGF (bevacizumab) in combination with standard chemotherapy in subjects with metastatic colorectal cancer (study # AVF2107g).

Nine hundred twenty-three subjects with metastatic colorectal cancer were randomized to one of three treatment arms:

Arm 1: irinotecan/5-FU/leucovorin (bolus-IFL) + placebo

Arm 2: bolus-IFL + rhuMAb VEGF

Arm 3: 5-FU/leucovorin + rhuMAb VEGF

Bevacizumab was given at a dose of 5 mg/kg every 2 weeks. Arms 1 and 2: Subjects received the bolus-IFL regimen, consisting of 125 mg/m^2 irinotecan by 90-minute IV infusion, 500 mg/m^2 5-FU by IV bolus injection, 20 mg/m^2 leucovorin by IV bolus injection. The drug was administered in repeating 6-week cycles consisting of weekly treatments for 4 weeks followed by 2 weeks of rest.

Arm 3: Subjects received 500 mg/m^2 5-FU by IV bolus (slow push) and 500 mg/m^2 leucovorin by 2-hour IV infusion, administered weekly for 6 weeks of each 8-week cycle.

The mean age of subjects was 59 years (range: 21 to 88 years). Sixty percent subjects were male and 79.6% of the subject population was white. Blood samples for determining irinotecan plasma levels were collected in a subset of 50 subjects in each of arms 1 and 2 to investigate irinotecan disposition in the presence and absence of rhuMAb VEGF. In addition, samples were collected in a subset of 300 subjects (100 subjects per arm) to determine rhuMAb VEGF disposition in the presence and absence of irinotecan. Blood samples were collected before and 10 minutes after study drug infusion at the following timepoints: screening, day 14 of cycle 1 (Arms 2 and 3), and day 0 of cycle 3 (Arm 2) or day 28 of cycle 2 (Arm 3). PK analyses were performed using serum concentration-time data from the two bevacizumab-containing treatment regimens (Arms 2 and 3) using nonlinear mixed-effects modeling. Because only peak and trough samples were collected, a one-compartment model was used for analysis. The results are summarized in Table 8.1

TABLE 8.1

Population pharmacokinetic parameters of bevacizumab

Model Features	Model
Number of evaluable subjects	214
Objective function	4758
Typical CL (mL/hr)	10.2 (2.80)
Typical V_c (mL)	3230 (2.00)
ω_{CL} (%)	30.8 (10.5)
ω_V (%)	18.7 (30.1)
σ_{Prop} (%)	12.4 (38.4)
σ_{Add} (µg/mL)	16.7 (18.3)

CL=clearance; V_c=central volume of distribution; σ_{Add}=residual variance (additive); σ_{Prop}=residual variance (multiplicative); ω_{CL}=variance of clearance; ω_V=variance of volume.

In this study, rhuMAb VEGF concentrations were similar when rhuMAb VEGF was combined with two regimens (5-FU/leucovorin and bolus-IFL), suggesting that the addition of irinotecan to 5-FU/leucovorin does not affect the pharmacokinetics of rhuMAb VEGF. Results of the current trial were compared with those of a previous study (AVF0780g), in which rhuMAb VEGF was administered at a dose of 5 mg/kg every 2 weeks. In Study AVF0780g, the day 14 mean trough concentration was 35.4 mcg/mL and in this study the mean trough concentrations on day 14 were 28.6 and 32.5 mcg/mL for Arms 2 and 3, respectively. Estimated pharmacokinetic parameters from the two studies were also consistent. In Study AVF0780g, using a one-compartment model, the mean clearance and volume of distribution were 2.79 mL/kg/day and 45.4 mL/kg, respectively. In the study, these parameters were 3.5 mL/kg/day and 46 mL/kg, respectively. Clearance was 20% higher in the current study as compared to Study AVF0780g.

Irinotecan concentrations were unaffected by rhuMAb VEGF administration. SN38 (active metabolite of irinotecan) concentrations were 33% higher among rhuMAb VEGF-treated subjects compared to control subjects. There was a high variability in the data. The mechanism by which rhuMAb VEGF might increase SN38 levels is unclear. Irinotecan is extensively metabolized into four major metabolites: SN38, SN38 glucuronide (SN38G), APC, and NPC. Carboxylesterase (in liver, intestine, and

plasma) and cytochrome P450 3A4 (in liver and intestine) are responsible for the metabolism of irinotecan into SN38, APC, and NPC. UDP glucuronosyl-transferase (UGT) is responsible for the glucuronidation of SN38 into the inactive metabolite SN38G which is excreted into bile. Deconjugation of SN38G to SN38 by glucuronidase produced by intestinal flora may contribute to enterohepatic recirculation of SN38.

The effect of irinotecan on bevacizumab CL was tested by comparing subjects receiving bevacizumab + 5-FU/leucovorin to those receiving bevacizumab + bolus-I FL. Clearance estimates for the two groups were similar, indicating that the addition of irinotecan to 5-FU/leucovorin/bevacizumab does not affect the pharmacokinetics of bevacizumab.

Comments:

The study design and sampling scheme is inadequate to determine whether or not there is an interaction between bevacizumab and irinotecan.

Study #9

Title: Population pharmacokinetics of bevacizumab: Structural model identification, mean population pharmacokinetic parameter estimation, and covariate analysis (non-GLP; Report #03-0324-1751).

The population PK analysis for bevacizumab was based on the pooled datasets from eight clinical studies including two Phase I studies, four Phase II studies, and two Phase III studies in subjects with several types of solid tumors. The analysis included a total of 4629 bevacizumab concentrations for 491 subjects who received IV infusion doses weekly, every 2 weeks, or every 3 weeks at doses ranging from1 to 20 mg/kg. In all studies, bevacizumab was administered initially as a 90-minute infusion. If this first infusion was well tolerated, the infusion duration could be decreased in increments of 30 minutes. The infusion duration was not to be shorter than 30 minutes. The studies included in the analysis are summarized in Table 9.1.

TABLE 9.1

Summary of studies included in population PK study

	Study	Bevacizumab Dose (mg/kg)	Dosing Frequency	Concomitant Chemotherapy	Sampling Scheme Frequency	Subjects with PK Data
Phase I						
—	Dose-escalation, solid tumors	1, 3, 10[a]	Once monthly, then weekly for 3 weeks	Single agent	Full profile[b]	25
—	Solid tumors	3	Weekly	Doxorubicin, carboplatin/paclitaxel, 5-FU/LV	Full profile[b]	12
Phase II						
—	Pilot —	10	Every 2 weeks	Single agent	Multiple peaks and troughs	15
—	Dose-escalation, MBC	3, 10, 20	Every 2 weeks	Single Agent	Multiple peaks and troughs	74
—	Combination, NSCLC	7.5, 15	Every 3 weeks	Carboplatin/paclitaxel	Multiple peaks and troughs	66
AVF0780g:	Combination, CRC	5, 10	Every 2 weeks	5-FU/LV	Multiple peaks and troughs	67
Phase III						
—	MBC	15	Every 3 weeks	Capecitabine	Multiple peaks and troughs	38
AVF2107g:	Combination, CRC	5	Every 2 weeks	5-FU/LV or 5-FU/LV/CPT-11	Peaks and troughs at 2 cycles	236

5-FU = 5-fluorouracil; CRC = Colorectal carcinoma; ; LV = Leucovorin; CPT-11 = Irinotecan.

[a] Doses of 0.1 and 0.3 mg/kg that were also investigated in this study in 10 patients were not included in the analysis because bevacizumab clearance at these doses was faster and these doses were not evaluated in further studies.

[b] Serial samples collected over 1 month after administration of either first or last dose.

Several covariates were used in the analysis. These include age, gender, race, height, body weight, body surface area, and lean body weight, creatinine clearance,

alkaline phosphatase, serum glutamic oxaloacetic transferase concentration, serum glutamic pyruvic transminase concentration, total bilirubin, total protein, albumin, and serum creatinine, combination chemotherapy. Body surface area, lean body weight, and creatinine clearance were estimated according to following equation:

BSA (m^2) was estimated as follows:

$$BSA = WT^{0.425} \times HT^{0.725} \times 71.84/10{,}000$$

where WT is the weight in kg and HT the height in cm.

LBW (kg) was estimated as follows:

In men: $LBW = 1.1 \times WT - 128 \times (WT^2/HT^2)$

In women: $LBW = 1.07 \times WT - 148 \times (WT^2/HT^2)$

CRCL (mL/min) was estimated using total body weight and lean body weight as follows (Cockcroft and Gault 1976):

In men: $$CRCL = \frac{(140 - age) \times WT \text{ in kg}}{(72 \times \text{serum creatinine})}$$

In women: $$CRCL = \frac{(140 - age) \times WT \text{ in kg}}{(72 \times \text{serum creatinine})} \times 0.85$$

The model-based PK analysis was performed using the NONMEM program (double precision, Version V, level 1.0; UCSF, San Francisco, CA) with an NM- TRAN preprocessor (Version III, level 1.0) and PREDPP routines (Version IV, level 1.0).

The basic models tested were one- and two-compartment structures with zero-order input (infusion). For the one-compartment model, the basic parameters were clearance (CL; L/day), central compartment volume of distribution (Vc; L). For the two-compartment model, the parameters were Vc, CL, and the intercompartmental rate constants (K_{12}, K_{21}; day-1). PREDPP subroutines ADVAN 1, TRANS 1 and ADV AN 3, TRANS 1 were used for the one- and two-compartment models, respectively. The time unit used in analysis was hour, so the units for CL, V_C, K_{12}, and K_{21} in NONMEM control file and output were mL/h, mL, hr^{-1}, and hr^{-1} respectively. Throughout the report, time units reported for PK parameters are in days. The residual variability was modeled

as additive/proportional error model. One or two-compartment models using the first order (FO) or the first-order conditional estimation (FOCE) were used to estimate population PK parameters. The two-compartment model was used for POSTHOC Bayesian estimate to obtain the PK parameters for individual subjects. The best structural model was a two-compartment model with first-order elimination. Table 9.2 summarizes the results of the population PK parameters for bevacizumab.

TABLE 9.2

Summary of Population Parameters with CV (%) for the Final PP Model and Final Model

Parameter	Final PP Model	Final Model (δ=–62.7)	Final Model FOCE	Final Model with CL–V_c Correlation (δ=–33.3)
MOF	37317.7	37255.0	37204.1	37221.7
Typical CL (L/day)	0.185 (4.0)	0.207 (4.6)	0.212 (4.3)	0.208 (4.6)
GDR on CL	0.235 (30.9)	0.264 (27.6)	0.269 (25.9)	0.268 (27.7)
WT on CL	0.370 (36.8)	0.368 (36.7)	0.378 (36.8)	0.353 (38.2)
ALBU on CL	–0.736 (20.5)	–0.726 (20.7)	–0.765 (20.4)	–0.739 (20.3)
ALK on CL	0.132 (30.8)	0.133 (26.4)	0.143 (26.4)	0.131 (26.3)
SGOT on CL	–0.0658 (55.8)	–0.0715 (48.5)	–0.0625 (57.3)	–0.0756 (46.3)
CHEM on CL (0 vs. 5)	NA	–0.003 (1630.5)	0.0281 (175)	–0.0112 (398)
CHEM on CL (1–4 vs. 5)	NA	–0.174 (22.1)	–0.179 (23.3)	–0.180 (21.1)
Typical V_c (L)	2.69 (1.8)	2.66 (1.7)	2.68 (1.6)	2.65 (1.6)
GDR on V_c	0.215 (13.4)	0.221 (13.2)	0.215 (12.8)	0.210 (13.7)
WT on V_c	0.413 (13.4)	0.411 (13.6)	0.408 (14.0)	0.410 (12.7)
ALBU on V_c	–0.341 (17.2)	–0.333 (17.2)	–0.329 (17.8)	–0.306 (19.0)
K_{12} (day^{-1})	0.214 (28.7)	0.223 (27.9)	0.264 (25.5)	0.205 (28.9)
K_{21} (day^{-1})	0.200 (24.0)	0.215 (22.9)	0.262 (20.7)	0.201 (23.7)
ω_{CL} (%)	24.1 (11.8)	26.0 (14.0)	26.8 (15.8)	25.6 (14.1)
ω_{Vc} (%)	17.1 (15.2)	16.8 (14.2)	16.3 (13.0)	16.1 (13.3)
Correlation (η_{Vc}, η_{CL})	NA	NA	NA	0.39
σ_{prop} (%)	17.5 (9.0)	17.2 (8.4)	17.3 (8.3)	17.1 (8.4)
σ_{add} (µg/mL)	7.6 (56.3)	7.2 (60.8)	7.0 (63.0)	7.3 (59.8)
K_{10} (day^{-1})	0.0688	0.0779	0.0792	0.0786
$t_{1/2\alpha}$ (days)	1.53	1.44	1.22	1.54
$t_{1/2\beta}$ (days)	22.8	19.9	19.0	19.7

PP = Patho-physiological model

Based on the population analysis, clearance and volume in an individual subject can be calculated from the following equation:

$$CL = CL \times (WT/74)^{0.368}$$

Where CL = 0.262 L/day for males and 0.207 L/day for females.

$$V = V \times (WT/74)^{0.411}$$

Where V = 3.25 L for males and 2.66 L for females.

In the final model, of the 17 covariates tested, body weight, gender, albumin, alkaline phosphatase, SGOT, and chemotherapy were the only covariates that were significantly associated with bevacizumab disposition. Based on the final model (chosen based on the minimum objective function), clearance was 0.262 and 0.207 L/day for a typical male and female subject, respectively. The volume of distribution of the central compartment (V_c) was 3.25 and 2.66 L in male and female subjects, respectively. The estimated half-life was approximately 20 days. Body weight was an important covariate affecting bevacizumab CL and volume. There was no correlation between bevacizumab clearance and age. Gender seems to have impact on clearance and volume. The clearance and volume is 21% and 18% lower in the females than the males, respectively. After correcting for body weight, male subjects had a higher bevacizumab clearance (26%) and a larger Vc (22%) than females. However, this difference may not be of any clinical significance.