CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN-125085/0

Pharmacology Review(s)

BLA STN #125085

REVIEW AND EVALUATION OF PHARMACOLOGY DATA

Bevacizumab (AVASTIN®)

Genentech, Inc.
South San Francisco, CA

Reviewer:
Anita M. O'Connor, Ph.D.

Division of Therapeutic Internal Medicine Products (HFM-576)
Center for Drug Evaluation and Research
Food and Drug Administration

2/25/04

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Executive Summary

1. Recommendations

1.1 Recommendation on approval

Bevacizumab is recommended for approval.

1.1 Recommendation for nonclinical studies

No additional nonclinical studies of bevacizumab are recommended at the present time.

1.2 Recommendations on labeling

The sponsor has proposed the following (in italics) for the label in the first paragraph of the Clinical Pharmacology section (page 2 of 20):

CLINICAL PHARMACOLOGY
General

[redacted]

Recommended changes to the wording of this paragraph in the package insert are:

CLINICAL PHARMACOLOGY
Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of Bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

1.2 Summary of nonclinical findings

Pharmacokinetic studies were conducted in nude (athymic) mice, rats, rabbits, and cynomolgus monkeys. In the latter (most relevant) species, elimination half-life ranged from 8-10 days, clearance was 4.76-5.78 mL/day/kg, and time to maximum serum concentration was 5-33 minutes over the 2, 10, and 50 mg/kg IV dose range. Absorption and maximum serum concentrations were dose proportional.

Rabbits were used to study the biodistribution of the radiolabeled product. The product was mainly distributed to the vascular space with limited distribution to

the tissues. The distribution and elimination of the product was similar to the control article, rhuMAb E25.

Two pivotal drug interaction studies were conducted in cynomolgus monkeys. The first study evaluated the pharmacokinetics of Bevacizumab upon administration of cisplatin and Taxol®. It was found that the pharmacokinetics of Bevacizumab were not altered in the presence of cisplatin and Taxol®. Conversely, the pharmacokinetics of Taxol® and cisplatin were not altered by the administration of rhuMAb VEGF. The second study, a smaller pilot study, evaluated the pharmacokinetics of Bevacizumab with Irinotecan, 5-Fluorouracil and Leucovorin. No pharmacokinetic drug interactions occurred in this study.

1.3 Brief overview of nonclinical findings

The BLA submission contains pharmacology, pharmacokinetic, and toxicology sections. The pharmacology section consists of 27 published articles and 13 original studies (see Appendix I).

1.4 Pharmacologic activity

Recombinant humanized monoclonal antibody to VEGF (rhuMAb VEGF) is a humanized monoclonal IgG kappa antibody directed against human vascular endothelial growth factor. Vascular endothelial growth factor (VEGF) is a endothelial specific mitogen, mediated by two tyrosine kinase receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2). VEGF is a regulator of angiogenesis. It is critical for growth and development of vascular and lymphatic endothelial cells. The VEGF family is composed of VEGF, placenta growth factor, VEGF-B, VEGF-C, and VEGF-D.

The sponsor's product, rhuMAb VEGF, does not have high binding affinity to mouse or rat VEGF. However, it is pharmacologically active in the cynomolgus monkey.

1.5 Nonclinical safety issues relevant to clinical use

VEGF is critical for embryonic vasculogenesis, bone formation, and the physiology of the female reproductive tract, all processes dependent upon proliferation of new blood vessels.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: STN BLA-125085
Sequence number/date/type of submission: STN BLA #125085\0; September 2, 2003
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: GENENTECH
Manufacturer for drug substance: GENENTECH

Reviewer name: Anita M. O'Connor, Ph.D.
Division name: Division of Therapeutic Biological Internal Medicine Products
HFM #: 576
Review completion date: February 23, 2004

Drug:

Trade name: Avastin®
Generic name: Bevacizumab
Code name: G180CL, G180CU, G180DL (Drug Product)
Chemical name: Recombinant humanized monoclonal antibody to VEGF
CAS registry number: #-216974-75-3
Molecular formula/molecular weight: 149,199 Daltons
Structure: See figures 1 and 2 below

Figure 1
Primary Sequence of Bevacizumab

[

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The residues underlined are part of the complementarity-determining regions of the antibody (Presta et al. 1997).

Figure 2
Primary Sequence of Bevacizumab

[

]

The residues underlined are part of the complementarity-determining regions of the antibody (Presta et al. 1997).

Relevant INDs/NDAs/DMFs: BB IND #7023 (Genentech) and BB IND #7921 (NCI)

Drug class: Monoclonal antibody

Indication: AVASTIN® (bevacizumab) in combination with 5-fluorouracil-based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon and rectum.

Clinical formulation:
AVASTIN® is supplied as a sterile liquid in 4 mL and 16 mL, single use glass vials designed to deliver 100 and 400 mg of bevacizumab per vial, respectively.

Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN® (25 mg/mL). The formulation is 25 mg/mL bevacizumab in 51 mM sodium phosphate, pH 6.2, 60 mg/mL trehalose dihydrate, and 0.04% polysorbate 20.

Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN®(25 mg/mL). The formulation is 25 mg/mL bevacizumab in 51 mM sodium phosphate, pH 6.2, 60 mg/mL trehalose dihydrate, and 0.04% polysorbate 20.

Route of administration: The proposed package insert states: [

[

]

Proposed use: The proposed package insert states: [

]

Disclaimer: The primary sequence structures, figures, tables, and the list of pharmacologic/pharmacokinetic studies are graphic images taken from the submission.

Studies reviewed within this submission: BLA sections 4.2.1 (Pharmacology) and 4.2.2. (Pharmacokinetics). For a review of section 4.2.3 (Toxicology) see review by Dr. Barbara Wilcox.

Studies not reviewed within this submission: Analytical Methods and Validation Reports (Section 4.2.2.1) and Toxicology (Section 4.2.3)

3.2 PHARMACOLOGY

3.2.1 Brief summary

3.2.2 Primary pharmacodynamics
This section consists of 19 published articles from the scientific literature in portable document format.

3.2.3 Secondary pharmacodynamics
No studies of this type are included in the submission.

3.2.3 Safety pharmacology
No studies of this type are included in the present submission.

3.2.5 Pharmacodynamic drug interactions

This section consists of 8 published articles from the scientific literature in portable document format.

3.3 PHARMACOKINETICS/TOXICOKINETICS

Thirteen pharmacokinetic studies are in section 4.2 of the submission (see Appendix I for a list of studies)

3.3.1 Brief summary

Pharmacokinetic studies were conducted in nude (athymic) mice, rats, rabbits, and cynomolgus monkeys. In the latter (most relevant) species, elimination half-life ranged from 8-10 days, clearance was 4.76-5.78 mL/day/kg, and time to maximum serum concentration was 5-33 minutes over the 2, 10, 50 mg/kg IV dose range. Absorption and maximum serum concentrations were dose proportional.

Rabbits were used to study the biodistribution of the radiolabeled product. The product was mainly distributed to the vascular space with limited distribution to the tissues. The distribution and elimination of the product was similar to the control article, rhuMAb E25.

Two pivotal drug interaction studies were conducted in cynomolgus monkeys.
The first study evaluated the pharmacokinetics of Bevacizumab upon administration of cisplatin and Taxol®. It was found that the pharmacokinetics of Bevacizumab were not altered in the presence of cisplatin and Taxol®. Conversely, the pharmacokinetics of Taxol® and cisplatin were not altered by the administration of rhuMAb VEGF. The second study, a smaller pilot study, evaluated the pharmacokinetics of Bevacizumab with Irinotecan, 5-Fluorouracil and Leucovorin. No pharmacokinetic drug interactions occurred in this study.

3.3.3 Absorption

Study: ***Pharmacokinetic Analysis: rhuMAb VEGF Intravenous and Intraperitoneal Pharmacokinetics of rhuMAb VEGF in Female NU/NU (athymic) Nude Mice***

Key study findings: The product is not pharmacologically active in this species. The study complemented the proof of concept (i.e., xenotransplant efficacy) studies done in this strain of mice. Key study findings are found under pharmacokinetic results (below).
Study no.: 96-416-1751PK
Volume #, and page #: N/A (electronic submission)
Conducting laboratory and location: Genentech
Date of study initiation: December 16, 1996
GLP compliance: Not specified in final report
QA statement: yes ( ) no (X)
Drug, lot #, and % purity: rhuMAb VEGF, Lot No. M3-RD595 rhuMAb VEGF Vehicle: Lot No. M3-RD488; information regarding the purity was not provided in the final study report.

Methods

Doses: .80 mg/kg IP, .80 mg/kg IV, 8.5 mg/kg IP, 8.5 mg/kg IV (see table in Appendix II)
Species/strain: Athymic female NU/NU mice, weighing 16-25 grams
Number/sex/group: 2 per treatment group per time point (n=90)
Route, formulation, volume, and infusion rate: Single intraperitoneal (IP) or IV
Satellite groups: None
Study design: Single injection for pharmacokinetic evaluation; 2 mice sacrificed at each time point (0, 1, 2, 4, 8, 16, 24 and 32 hours, and days 2, 3, 5, 8, 11, 14, 17)
Parameters and endpoints evaluated: rhuMAb VEGF serum concentrations by ELISA for pharmacokinetic endpoints

Results

Mortality: None cited
Clinical signs: Not done
Body weights: Not done
Food consumption: Not done
Toxicokinetics: Not done
Pharmacokinetics: The maximum serum concentration for the IV groups was approximately dose proportional and absorption (AUC) was dose dependent. The IP data were highly variable. Due to ambiguous results the experiment was repeated. (See Table 1 and Figure 1, Appendix II, for pharmacokinetic data.)

Study: ***Pharmacokinetic Analysis: rhuMAb VEGF Intravenous and Subcutaneous Pharmacokinetics of rhuMAb VEGF in Female Mice***

Key study findings: The product is not pharmacologically active in this species. This study complemented the proof of concept (e.g., xenotransplant efficacy) studies conducted with this strain of mice. The pharmacokinetic parameters are in the same range of those in the previous study (96-195-1751PK) for the 8.5 mg/kg IV treatment group.
Study no.: 96-195-1751PK
Volume #, and page #: N/A (electronic submission)
Conducting laboratory and location: Genentech
Date of study initiation: June 19, 1996
GLP compliance: Not specified
QA statement: yes ( ) no (X)
Drug, lot #, and % purity: Lot and purity were not specified in the final report

Methods

Doses: 9.3 mg/kg IV or 9.3 mg/kg subcutaneous (SC)
Species/strain: Beige nude mice (n=60), body weight range=19-25 grams
Number/sex/group: 2/treatment/timpoint

Route, formulation, volume, and infusion rate: 0.14 mL of 1.45 mg/mL of rhuMAb VEGF either as a single IV or SC injection (9.3 mg/kg)
Satellite groups: None
Study design: Single injection for pharmacokinetic evaluation; serum was harvested on day 1 at 5 minutes, 1, 2, 4, and 8 hours, on day 2 at 0 and 8 hours, and on days 3, 4, 5, 6, 9, 12, and 15. At each time point, two mice per group were sacrificed. In addition, two mice were sacrificed for predose sampling.
Parameters and endpoints evaluated: rhuMAb VEGF serum concentrations (by ELISA) for pharmacokinetic endpoints

Results
Mortality: None cited
Clinical signs: Not done
Body weights: Not done
Food consumption: Not done
Toxicokinetics: Not done
Pharmacokinetics: Estimates of error, (as standard deviations or standard errors) were not reported. Absorption ($AUC_{0-\infty}$) was 593 and 682 ug•day/mL for the IV and SC treatment groups, respectively. Mean residence time was approximately 8-10 days for both groups. Terminal half-lives were similar for both groups (~6-7 days). Weight normalized serum clearance (CL) was also similar for both treatment groups (15.7 and 13.6 mL/day/kg, respectively for IV and SC groups). Time of average observed peak concentration (T_{max}) was 5 minutes by IV and 32 hours by SC route of administration. Average observed peak rhuMAb VEGF (C_{max}) was roughly twice as high for the IV group (174 ug/mL) as the SC group (74.1 ug/mL). (See pharmacokinetic parameter estimates in Table 1, Appendix III.)

Study: ***Pharmacokinetic Analysis: rhuMAb VEGF Pharmacokinetics of rhuMAb VEGF in Male Rats***

Key study findings: With the exception of T_{max}, the pharmacokinetic parameters were not within the same range as those seen in the athymic mouse studies. The relationship between dose and pharmacokinetic parameters was not dose proportional (i.e., not linear). However, the study is not very informative due to small numbers of animals, lack of pharmacological activity and the limited sampling schedule.
Study no.: 96-196-1751PK
Volume #, and page #: N/A (electronic submission)
Conducting laboratory and location: Genentech
Date of study initiation: June 19, 1996
GLP compliance: Not specified
QA statement: yes ( ) no (X)
Drug, lot #, and % purity: Lot and purity were not specified in the final report

Methods
Doses: 1 or 10 mg/kg of rhuMAb VEGF by IV or 10 mg/kg SC (see study design table in Appendix IV)
Species/strain: Sprague Dawley rats weighing 297-345 grams

Number/sex/group: 3 per group (n=9)
Route, formulation, volume, and infusion rate: Each group received either an IV or SC injection of rhuMAb VEGF. Actual doses received were 0.664 mg/kg or 10.1 mg/kg as a single IV bolus in the femoral vein or 10.1 mg/kg as a single SC injection in the flank. Actual dose concentrations were 0.521 and 7.93 mg/mL.
Satellite groups: None
Study design: Serum was harvested from each rat prior to dosing and on day 1 at 5, 15, and 30 minutes post-dose, 1, 2, 4, 6 and 8 hours, on day 2 at 0 and 8 hours, and on days 3, 4, 5, 8, 9, 10, 12, and 15.
Parameters and endpoints evaluated: rhuMAb VEGF serum concentrations (by ELISA) for pharmacokinetic endpoints

Results
Mortality: None cited
Clinical signs: Not done
Body weights: Not done
Food consumption: Not done
Toxicokinetics: Not done
Pharmacokinetics: For group 2, administered 10.1 mg/kg by IV, (mean) T_{max} was 5 (minutes), C_{max} was 341±39 (ug/mL), CL was 4.83±1.1 (mL/day/kg), elimination half-life was 12.3±3.2 (days) and $AUC_{0-\infty}$ (ug•day/mL) was 2160±500. For group 1, administered 0.664 mg/kg by IV, T_{max} was 15 (minutes), C_{max} was 29.7±1.8 (ug/mL), CL was 8.37±1.4 (mL/day/kg), elimination half-life was 5.42±.82 (days) and $AUC_{0-\infty}$ (ug•day/mL) was 80±14.

Standard deviations indicated high variability due to low animal numbers. Limited sampling (i.e., only two half-lives) also compromise the results of this study. (See Table 1 and Figure 1 in Appendix IV for pharmacokinetic parameter estimates and graphs.)

Study: ***Single Intravenous/Subcutaneous Dose Pharmacokinetic Study with rhuMAb VEGF in Male Cynomolgus Monkeys***

Key study findings: The pharmacokinetics of rhuMAb VEGF in cynomolgus monkeys was dose proportional (i.e. linear).
Study no.: 96-211-1751
Volume #, and page #: N/A (electronic submission)
Conducting laboratory and location: ——
Date of study initiation: October 3, 1996
GLP compliance: Yes
QA statement: yes (X) no ( )
Drug, lot #, and % purity: rhuMAb VEGF Lot M3-RD595, vehicle Lot. M3-RD588, product purity characteristics were , ——— and SDS-PAGE= expected banding pattern

Methods

Doses: 2, 10, 50 mg/kg IV (5 mL volume) or 10 mg/kg SC (1 mL volume) (see study design table in Appendix V)

Species/strain: Cynomolgus monkeys
Number/sex/group: 4 males/treatment group (n=16)
Route, formulation, volume, and infusion rate: For the 3 IV treatment groups infused over 10-30 seconds the volume was 5 mL; the SC group received a 1 mL volume infused as a bolus injection
Satellite groups: None
Study design: Each group received either a single dose IV or SC for pharmacokinetic endpoints and antibody formation to the product. Animals were sampled for rhuMAb VEGF pre dosing, and at 5 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 36 hours, and days 3-16, 18, 21, 24, 27, 30; antibody analyses were done at week –3, pre dosing day 1 and on day 30.
Parameters and endpoints evaluated: rhuMAb VEGF serum concentrations (by ELISA) for pharmacokinetic endpoints, IgG antibodies (by ELISA) to rhuMAb VEGF

Results
Mortality: None
Clinical signs: No observations of clinical toxicity
Body weights: Normal
Food consumption: Normal
Clinical Pathology: Normal, although animals were only evaluated at -12 days
Toxicokinetics: Not done
Immunogenicity: No IgG antibodies to the product were detected; however, one animal did have a precipitous drop in serum rhuMAb VEGF after day 18 for unknown reasons.
Pharmacokinetics: The pharmacokinetics of rhuMAb VEGF in cynomolgus monkeys was dose proportional (i.e. linear). Time to maximum serum concentration for the 2 and 10 mg/kg IV groups was 18 and 33 minutes, respectively. The elimination half-life ranged from 8.75 to 10.3 days for the 2, 10, and 50 mg/kg IV groups. Clearance corrected for body weight was also similar between these groups, ranging from 4.76 to 5.78 mL/day/kg. The mean residence time for the IV groups was 12-13.4 days. Absorption was 430, 1810, and 8800 (ug/day/mL) for the 2, 10, and 50 mg/kg IV groups. Maximum serum concentration, also dose proportional, was 68, 290, and 1400 for these three groups. (See tables and Figure 1 in Appendix V showing pharmacokinetic estimates and serum concentrations over time.)

3.3.4 Distribution

Study: ***Tissue Distribution of ^{125}I-rhuMAb VEGF in Rabbits Following Intravenous Administration***

Key study findings: The product was primarily distributed in the vascular space with limited distribution to tissues. Tissue uptake and catabolism were similar between rhuMAb VEGF and the control article, rhuMAb E25.
Study no.: 96-323-1751
Volume #, and page #: N/A (electronic submission)
Conducting laboratory and location: Genentech, Inc.
Date of study initiation: September 24, 1996

GLP compliance: No
QA statement: yes ( ) no (X)
Drug, lot #, and % purity: GNE 24748-93 (rhuMAb VEGF) and C9810AX (rhuMAb EGF E25)
Methods

Doses: See study design table in Appendix VI; trace doses of either rhuMAb EGF E25 or rhuMAb VEGF were administered (~5 ug/kg protein dose; 464-652 mCi/kg of ^{125}I labeled dose; 95 or 125 uCi/mg specific activity)
Species/strain: Rabbit, New Zealand White, 5 weeks old, 1.1-1.3 kg
Number/sex/group: 2 males per treatment group (n=8)
Route, formulation, volume, and infusion rate: Single IV bolus
Satellite groups: None
Study design: Blood was collected at 2, 5, 8, 24, 32, and 48 hours prior to sacrifice.
Parameters and endpoints evaluated: Radioactivity analysis of plasma, urine and tissues

Results
Mortality: None cited
Clinical signs: Not done
Body weights: Not done
Food consumption: Not done
Toxicokinetics: Not done
Pharmacokinetics: The profile of radioactive plasma rhuMAb VEGF and rhuMAb VEGF E25 were similar, especially at the 2, 5, and 8 sampling points. (See Figure 2 Appendix VI.)
Tissue Distribution: Less than 10% of the radioactivity in the urine was precipitable suggesting that most of the urine radioactivity was not proteinaceous. The primary route of excretion of the radioactivity was urinary. Both products were mainly found in the blood/plasma component and neither had significant uptakes by any organ, with the exception of rhuMAb VEGF E25 that appeared to have some unusually high uptake by lung tissue compared to rhuMAb VEGF at the 2 hour time point. The pattern of distribution was similar between the two products, (with the exception of the lung) suggesting no differences in catabolism and elimination (i.e. typical catabolism for a monoclonal antibody.) (See Figures 4A, 4B, 5A, 5B in Appendix VI.)

3.3.5 Metabolism

3.3.6 Excretion

3.3.7 Pharmacokinetic drug interactions

Study: ***Safety and Pharmacokinetics of rhuMAb VEGF Administered in Combination with Platinol ® -AQ and Taxol ® in Cynomolgus Monkeys***

Key study findings: The test article had no effects on the pharmacokinetics of either chemotherapy agent tested.

Study no.: 96-375-1751
Volume #, and page #: N/A (electronic submission)
Conducting laboratory and location: ——
Date of study initiation: November 25, 1996
GLP compliance: Yes
QA statement: yes (X) no ( )
Drug, lot #, and % purity: rhuMAb VEGF Lot No. M3-RD595, rhuMAb VEGF Vehicle, Lot No. M3-RD588, Platinol®-AQ [Cisplatin Injection, USP (cisplatin), Bristol-Myers Squibb Company, New Brunswick, New Jersey], Lot No. H6F28A, Paclitaxel for Injection Concentrate [(Taxol®), Bristol-Myers Squibb Company], Lot No. H6F29A

Methods

Doses: 0 or 10 mg/kg rhuMAb VEGF, 0 or 1 mg/kg cisplatin, 0 or 4 mg/kg Taxol® (see study design table in Appendix VII)
Species/strain: Cynomolgus monkeys
Number/sex/group: 5 animals assigned to 4 treatment groups (n=20)
Route, formulation, volume, and infusion rate: Intravenous via the saphenous vein
Satellite groups: None
Study design: See study design table in Appendix VII
Parameters and endpoints evaluated: Body weight, physical examinations, electrocardiographs, clinical chemistry, hematology, urine chemistry, cisplatin, Taxol®, and rhuMAb VEGF for pharmacokinetic endpoints, antibodies to rhuMAb VEGF

Results

Mortality: None
Clinical signs: No effects due to rhuMAb VEGF; vomiting in the chemotherapy groups
Body weights: No effects due to rhuMAb VEGF; lower body weights in the chemotherapy groups
Clinical Chemistry/Hematology: No effects due to rhuMAb VEGF; neutropenia in the chemotherapy groups
Food consumption: No effects due to any treatment, however, only qualitative (observational) data were collected
Toxicokinetics: Not done
Antibody Analyses: No anti rhuMAb VEGF antibodies were found in any monkey
Pharmacokinetics: See tables and figures in Appendix VII. rhuMAb did not appear to have any effects on the pharmacokinetics of either chemotherapy agent.

Study: ***Two-Week Pilot Intravenous Toxicity and Toxicokinetic Study with rhuMAb VEGF in Combination with Irinotecan, 5-Fluorouracil, and Leucovorin in Cynomolgus Monkeys***

Key study findings: See results (below). Treatment with rhuMAb VEGF did not appear to increase or decrease the effects related to treatment with the antineoplastic therapy regimen of Irinotecan (CPT-11), 5-Fluorouracil (5-FU), and Leucovorin (LV).

Study no.: 00-376-1756
Volume #, and page #: N/A (electronic submission)
Conducting laboratory and location: —
Date of study initiation: August 24, 2000
GLP compliance: Yes
QA statement: yes (Y) no ( )
Drug, lot #, and % purity: rhuMAb VEGF), Lot No. L9804AX, Camptosar Irinotecan HCl Injection (CPT-11), Lot No. 31DYH, Adrucil, Fluorouracil Injection (5-FU), Lot No. FFB099, Leucovorin Calcium for Injection LV Lot No. 426-080

Methods

Doses: See table in Appendix VIII
Species/strain: Young adult näive male cynomolgus monkeys, 2.6-3.4 kg
Number/sex/group: 4 males (group 1), 5 males (group 2), 3 males (group 3)
Route, formulation, volume, and infusion rate: Bolus IV for all drug products, right or left saphenous vein, excepting CP-11 (90 minute infusion)
Satellite groups: None
Study design: See table in Appendix VIII; animals were given human clinical doses of antineoplastic therapy. CP-11 was administered on days 1 and 8. Following CP-11 infusion, animals were dosed IV with LV, 5-FU, and rhuMAb VEGF.
Parameters and endpoints evaluated: Clinical signs, body weights, food consumption, toxicokinetics, clinical chemistry, hematology, macroscopic and microscopic pathology

Results

Mortality: None
Clinical signs: Vomiting, diarrhea in all groups attributed to chemotherapy
Body weights: Slight weight loss in all groups due to chemotherapy
Food consumption: Decreased feed intake attributed to chemotherapy
Clinical Chemistry: No biologically significant changes
Hematology: Red blood cells, hemoglobin, hematocrit, platelets declined in all groups due to chemotherapy and in response, percent reticulocytes increased. The decline in the red blood cell variables were partly due to repeated blood draws.
Toxicokinetics: No apparent effects of rhuMAb VEGF on the pharmacokinetics of CPT-11 or 5-FU. Following administration of CPT-11/5-FU/ the pK of CPT-11 and 5-FU was characterized by a rapid clearance with a half-life of approximately 1 hour and 0.5 hour, respectively. Pharmacokinetics of Leucovorin was not presented. The sponsor had assay problems with the primary metabolite of CPT-11 (SN38).
Pathology: Anatomical pathology findings related to administration of CPT-11, 5-FU, and LV included small thymus in Groups 1 and 2, thymic lymphoid depletion, and sternal myeloid hypoplasia and/or erythroid hyperplasia in all groups.

3.3.8 Other Pharmacokinetic Studies

Study Number	Title	Summary
99-023-1751 (Non-GLP)	Pharmacokinetic Study of rhuMAb VEGF (First and Second generation; full-length) Following Intravenous Administration in Normal Rabbits	The purpose of this study was to evaluate and compare the pk of two rhuMAb VEGF molecules, a first and second generation rhuMAb VEGF, following intravenous (IV) administration in female rabbits. Group 1 and 2 were administered 0.5 mg/kg of either first or second generation rhuMAb as a single bolus IV infusion. A third group was treated with 0.25 mg/kg of the second generation product. Antibodies were detected in the rabbits starting at day 4 after infusion, making the pharmacokinetics of the study not particularly informative.
98-055-1751 (Non-GLP)	Pharmacokinetic Study of [^{125}I] $VEGF_{165}$:rhuMAb VEGF Complexes Intravenously Administered in Normal Rats	Sprague-Dawley rats were administered a single IV bolus dose of either recombinant humanized VEGF165 (VEGF165), pre-formed $VEGF_{165}$:rhuMAb VEGF complexes (1:10 molar ratio), or rhuMAb VEGF alone. Clearance of the complexes was decreased by a factor of 3.4 compared to VEGF alone. Clearance of rhuMAb alone was similar to that of the complexes.
99-119-1751 (Non-GLP)	Pharmacokinetic Study of Two rhuMAb VEGF Cell-lines (current vs. new) Intravenously Administered in Normal Rats	The objective of this study was to characterize and compare the pharmacokinetics of rhuMAb VEGF from two different cell lines (rhuMAb VEGF control Lot H9815A and rhuMAb VEGF G7 Lot K9808A) following IV bolus administration of 10 mg/kg in 12 rats. Results suggested no differences between the 2 cell line products, however, a formal bioequivalency analysis was not conducted.
01-456-1751 (Non-GLP)	Pharmacokinetic Study of rhuMAb VEGF Intravenously Administered in Normal Rats	The purpose of this study was to characterize and compare the pk of 2 rhuMAb VEGF lots that were used in the preclinical cynomolgus monkey studies. All but 1/32 rats completed the IV dosing regimen with 10 mg/kg of either product lot. Following a single IV bolus dose at 10 mg/kg, the clearance of the 2 lots met the criterion for bioequivalence, with a geometric mean ratio of 0.944 and 90% CI of 0.83-1.06.
02-249-1751 (Non-GLP)	Pharmacokinetic Study of rhuMAb VEGF Intravenously Administered in Normal Rats	This study was designed to investigate and compare the pharmacokinetics and immunogenicity of rhuMAb VEGF used in Phase III (Lot N9832A) versus a subsequently manufactured lot (Lot R9844). Pharmacokinetic data were collected from 10 males/10 females per treatment group (n=40 total). Forty Sprague-Dawley rats completed the IV bolus single dose (10 mg/kg) study. Since animals developed antibodies to the product(s) after day 11, only pk data for days 1-11 were used in the analysis. Following a single IV bolus dose at 10 mg/kg, the clearance of rhuMAb VEGF Lot 1 and rhuMAb VEGF Lot 2 was similar and met the criterion for bioequivalence, with a geometric mean ratio (Lot 2 to Lot 1) of 0.98 and 90% CI of 0.9-1.06 for AUC_{0-11}.
99-079-1751 (Non-GLP)	Pharmacokinetic Study of rhuMAb VEGF Variants Intravenously Administered in Normal Rats	The purpose of this study was to characterize and compare the pharmacokinetics of two rhuMAb VEGF variant molecules, having differing glycosylation patterns, with a control lot of rhuMAb VEGF. None of these materials were used in clinical trials. There were low numbers of rats per group (n=15, or 3/treatment group); there were no differences in pharmacokinetics between groups.

3.3.10 Tables and figures to include comparative TK summary

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:
Genetic toxicology:

Carcinogenicity:
Reproductive toxicology:
Special toxicology:

3.4.2 Single-dose toxicity

3.4.3 Repeat-dose toxicity

3.4.4. Genetic toxicology

3.4.5. Carcinogenicity

3.4.6. **Reproductive and developmental toxicology**

3.4.7 Local tolerance

3.4.8 Special toxicology studies

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Unresolved toxicology issues (if any): None.

Recommendations: No further action is recommended for this product.

Suggested labeling:
See item 1.2 on page 3 of this review.

Signatures (optional):

Reviewer Signature /S/ 2-25-04

Supervisor Signature /S/ Concurrence Yes ✓ No ___
2-25-04

3.7. APPENDIX/ATTACHMENTS

APPENDIX I

LIST OF PHARMACOLOGY/PHARMOCOKINETIC STUDIES

4.2.2.2 Absorption

96-416-1751PK: Pharmacokinetic Analysis: rhuMAb VEGF Intravenous and Intraperitoneal Pharmacokinetics of rhuMAb VEGF in Female NU/NU (Athymic) Nude Mice

96-195-1751PK: Pharmacokinetic Analysis: rhuMAb VEGF Intravenous and Subcutaneous Pharmacokinetics of rhuMAb VEGF in Female Mice

96-196-1751PK: Pharmacokinetic Analysis: rhuMAb VEGF Pharmacokinetics of rhuMAb VEGF in Male Rats

4.2.2.2 Absorption (cont'd)

96-211-1751: Single Intravenous/Subcutaneous Dose Pharmacokinetic Study with rhuMAb VEGF in Male Cynomolgus Monkeys

Supplemental Analysis 96-211-1751PK: Single Intravenous/Subcutaneous Dose Pharmacokinetic Study with rhuMAb VEGF in Male Cynomolgus Monkeys

4.2.2.3 Distribution

96-323-1751: Tissue Distribution of ^{125}I-rhuMAb VEGF in Rabbits Following Intravenous Administration

4.2.2.4 Metabolism

96-323-1751: Tissue Distribution of ^{125}I-rhuMAb VEGF in Rabbits Following Intravenous Administration

4.2.2.5 Excretion

96-323-1751: Tissue Distribution of ^{125}I-rhuMAb VEGF in Rabbits Following Intravenous Administration

4.2.2.6 Pharmacokinetic Drug Interactions

96-375-1751: Safety and Pharmacokinetics of rhuMAb VEGF Administered in Combination with Platinol®-AQ and Taxol® in Cynomolgus Monkeys

Supplemental Analysis 96-375-1751PK: Safety and Pharmacokinetics of rhuMAb VEGF Administered in Combination with Platinol®-AQ and Taxol® in Cynomolgus Monkeys

00-376-1756: Two-Week Pilot Intravenous Toxicity and Toxicokinetic Study with rhuMAb VEGF in Combination with Irinotecan, 5-Fluorouracil, and Leucovorin in Cynomolgus Monkeys

Supplement to 00-376-1756—DCN: 12-083-T1: Determination of Irinotecan and its Metabolite, SN-38, in Heparinized Cynomolgus Monkey Plasma Samples by HPLC

4.2.2.7 Other Pharmacokinetic Studies

96-416-1751PK: Pharmacokinetic Analysis: rhuMAb VEGF Intravenous and Intraperitoneal Pharmacokinetics of rhuMAb VEGF in Female NU/NU (Athymic) Nude Mice

96-195-1751PK: Pharmacokinetic Analysis: rhuMAb VEGF Intravenous and Subcutaneous Pharmacokinetics of rhuMAb VEGF in Female Mice

96-196-1751PK: Pharmacokinetic Analysis: rhuMAb VEGF Pharmacokinetics of rhuMAb VEGF in Male Rats

99-023-1751: Pharmacokinetic Study of rhuMAb VEGF (First and Second Generation; Full-Length) Following Intravenous Administration in Normal Rabbits

4.2.2.7 Other Pharmacokinetic Studies (cont'd)

96-211-1751: Single Intravenous/Subcutaneous Dose Pharmacokinetic Study with rhuMAb VEGF in Male Cynomolgus Monkeys

Supplemental Analysis 96-211-1751PK: Single Intravenous/Subcutaneous Dose Pharmacokinetic Study with rhuMAb VEGF in Male Cynomolgus Monkeys

98-055-1751: Pharmacokinetic Study of ^{125}I-VEGF$_{165}$:rhuMAb VEGF Complexes Intravenously Administered in Normal Rats

99-119-1751: Pharmacokinetic Study of Two rhuMAb VEGF Cell-Lines (Control vs. New) Intravenously Administered in Normal Rats

01-456-1751: Pharmacokinetic Study of rhuMAb VEGF Intravenously Administered in Normal Rats

02-249-1751: Pharmacokinetic Study of rhuMAb VEGF Intravenously Administered in Normal Rats

99-079-1751: Pharmacokinetic Study of rhuMAb VEGF Variants Intravenously Administered in Normal Rats

APPENDIX II

Group	rhuMAb VEGF Dose (mg/kg)	Route
1	8.5	IV
2	8.5	IP
3	0.80	IV
4	0.80	IP

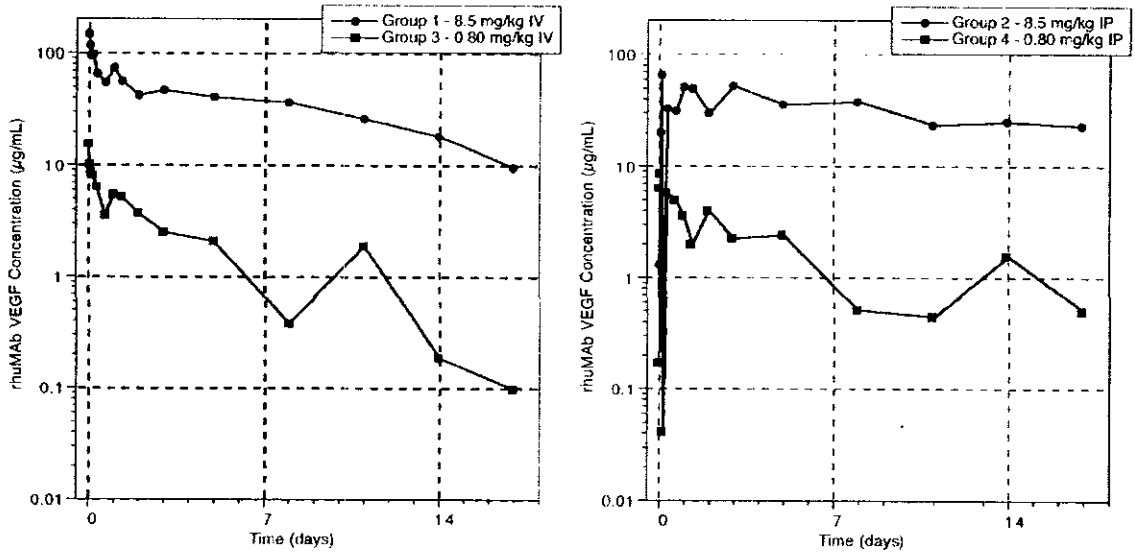
Table 1
Pharmacokinetic Parameter Estimates and Observed Parameters in Mice Following IV or IP Administration of 0.80 or 8.5 mg/kg rhuMAb VEGF

Group	1	2	3	4
Dose	8.5 mg/kg IV	8.5 mg/kg IP	0.80 mg/kg IV	0.80 mg/kg IP
Average Weight (g)	20.2	19.8	19.9	20.0
T_{max}	5 minutes	120 minutes	5 minutes	120 minutes
C_{max} (µg/mL)	148	65.6	15.6	8.58
CL/W (mL/day/kg)[a]	14.8	–[b]	34.1	–
$t_{1/2}$ elimination (day)	7.22	–	3.12	–
$AUC_{0-\infty}$ (µg-day/mL)	675	–	29.3	–
$AUC_{0\ min-Day17}$ (µg-day/mL)	575	553	28.9	27.1

[a] For IP dosing, clearance is CL/W/F where F is bioavailability.
[b] Due to the variable nature of the data following IP administration, the parameter is not reported.

Figure 1

Mean Serum rhuMAb VEGF Concentration versus Time Curves Following Intravenous or Intraperitoneal Administration of 0.80 or 8.5 mg/kg rhuMAb VEGF to Mice (n = 2 mice per timepoint per group)



APPENDIX III

Table 1
Pharmacokinetic Parameter Estimates and Observed Parameters in Female Mice Following IV or SC Administration of 9.3 mg/kg rhuMAb VEGF[a]

Parameters	9.3 mg/kg IV	9.3 mg/kg SC
Average Weight (g)	21.9	21.8
T_{max}[b]	5 min	32 hrs
C_{max} (µg/mL)[c]	174	74.1
V_c/W (mL/kg)[d]	53.0	119
V_{ss}/W (mL/kg)[e]	152	-[f]
CL/W (mL/day/kg)[g]	15.7	13.6
$t_{1/2}$ absorption (hr)[h]	-	6.19
$t_{1/2}$ α_1 (hr)	1.20	-
$t_{1/2}$ α_2 (day)	6.81	6.05
MRT (day)[i]	9.69	8.74
$AUC_{5min-Day15}$ (µg•day/mL)[j]	442	539
AUC (µg•day/mL)[k]	593	682
%AUCα_1	1.41	-
%AUCα_2	98.6	-
Bioavailability (%)[l]	-	110

a Parameters reported to two or three significant figures.

b Time of average observed peak concentration.

c Average observed peak rhuMAb VEGF concentration.

d V_c/W is the weight-normalized initial volume of distribution. For the SC group, this parameter is volume is V_c/F/W, where F is bioavailability.

e V_{ss} is the weight-normalized steady-state volume of distribution.

f Dashes = not applicable.

g Weight-normalized serum clearance. For the SC group, this parameter is CL/F/W, where F is bioavailability.

h $t_{1/2}$ absorption. $t_{1/2}$ α_1 and $t_{1/2}$ α_2 are the absorption half-life, initial half-life and terminal half-life, respectively.

i Mean residence time.

j Truncated area under the serum concentration versus time curve from 5 min. to Day 15.

k AUC is the extrapolated area under the serum concentration versus time curve; %AUCα_1 and AUCα_2 are the percent of AUC associated with each phase.

l Bioavailability determined from extrapolated AUC_{SC}/AUC_{IV}.

APPENDIX IV

Group	No. rats per group	Nominal Dose (mg/kg)	Route	Actual Dose Conc. (mg/mL)	Actual Dose (mg/kg)
1	3	1	IV	0.521	0.664
2	3	10	IV	7.93	10.1
3	3	10	SC	7.93	10.1

Table 1
Observed and Estimated Parameters in Male Rats Following IV or SC Administration of rhuMAb VEGF

	Group 1 - 0.664 mg/kg IV				Group 2 - 10.1 mg/kg IV				Group 3 - 10.1 mg/kg SC			
Parameter	Rat A	Rat B	Rat C	Mean ± SD	Rat D	Rat E	Rat F	Mean ± SD	Rat G	Rat H	Rat I	Mean ± SD
Weight (g)	332	325	345	334 ± 10	337	312	330	326 ± 13	297	301	313	304 ± 8.3
T_{max} [a]	15 min	30 min	15 min	15 min	15 min	5 min	5 min	5 min	7 days	7 days	4 days	7 days
C_{max} (µg/mL)		—		29.7 ± 1.8		—		341 ± 39		—		147 ± 13
V_C/W (mL/kg)[b]	24.0	25.5	25 5	25 0 ± 0.90	27.9	33.2	31.3	30.8 ± 2.7	36.3	27.0	28.0	30.5 ± 5.1
V_{ss}/W (mL/kg)	47.7	68.0	60.8	58.8 ± 10	68.9	76 2	93.2	79.5 ± 12	- [c]	-	-	-
CL/W (mL/day/kg)[d]	6.95	8 35	9.82	8 37 ± 1 4	5.88	3.74	4.86	4.83 ± 1 1	8 14	5 89	6.81	6 95 ± 1.1
$t_{1/2}\alpha_1$ (hr)[e]	5.08	8.70	8.70	7.49 ± 2.1	7.53	4 36	7.82	6.57 ± 1.9	74.2	76.3	68.5	73 0 ± 4 0
$t_{1/2}\alpha_2$(day)	4.98	6 37	4 92	5.42 ± 0.82	8.63	14.4	14.0	12.3 ± 3 2	3 09	3.18	2.86	3.04 ± 0 17
MRT (day) [f]	6.86	8.14	6.19	7.06 ± 0.99	11.7	20.4	19.2	17.1 ± 4.7	4 46	4.59	4.12	4.39 ± 0.24
$AUC_{5min-Day15}$ (µg-day/mL)[g]	82.7	62.9	61.4	69.0 ± 12	1200	1390	1130	1240 ± 130	1040	1400	1350	1260 ± 200
AUC (µg-day/mL)[h]	95 6	79 5	67.6	80.9 ± 14	1720	2700	2080	2160 ± 500	1240	1710	1480	1480 ± 240
$\%AUC\alpha_1$	4.81	12.1	13 8	10 2 ± 4.8	6.15	1.71	5.10	4.32 ± 2 3	-	-	-	-
$\%AUC\alpha_2$	95.2	87.9	86.2	89 8 ± 4.8	93.8	98 3	94.9	95.7 ± 2 3	-	-	-	-
Bioavailability (%) [i]	-	-	-	-	-	-	-	-	-	-	-	69

[a] T_{max} and C_{max} are the time of observed peak concentration and observed peak rhuMAb VEGF concentration, respectively.

[b] V_C/W and V_{ss}/W are the weight-normalized initial and steady-state volumes of distribution. For the SC group, volume is V_C/F/W, where F is bioavailability.

[c] Dashes = not applicable.

[d] Weight-normalized serum clearance. For the SC group, this parameter is CL/F/W, where F is bioavailability.

[e] $t_{1/2}\alpha_1$ and $t_{1/2}\alpha_2$ are the initial half-life (or absorption half-life for the SC group) and terminal half-life, respectively.

[f] Mean residence time.

[g] Truncated area under the serum concentration versus time curve (AUC) from 5 min to Day 15.

[h] Extrapolated area under the serum concentration versus time curve; $\%AUC\alpha_1$ and $AUC\alpha_2$ are the percent of AUC associated with each phase.

[i] Bioavailability determined from extrapolated AUC_{SC}/AUC_{IV} at a dose of 10.1 mg/kg.

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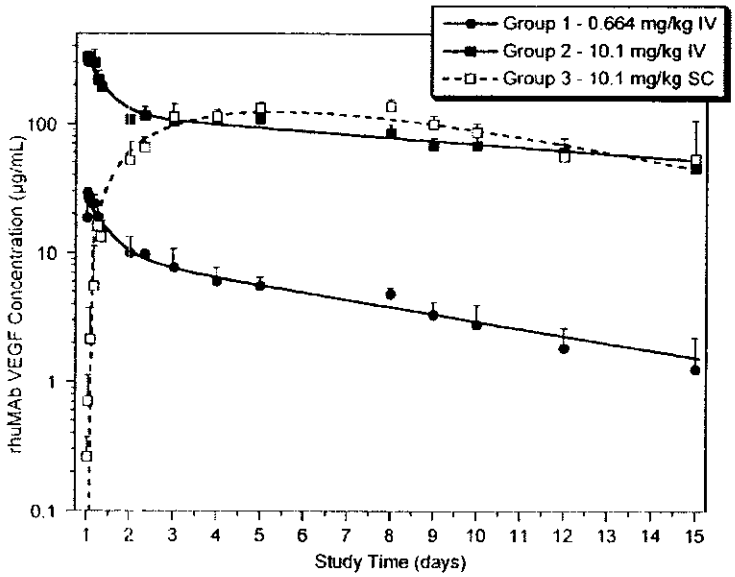
Figure 1

Group Mean (+ SD) rhuMAb VEGF Serum Concentration versus Time Curves Following Intravenous or Subcutaneous Administration of rhuMAb VEGF to Male Rats with the Mean Model Equation Superimposed on the Data (n=3 per timepoint)



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APPENDIX V

Group	Number of Males	Dose (mg/kg)	Route of Administration	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	
					Nominal	Actual
1	4	2	IV	5	0.4	0.407
2	4	10	IV	5	2	1.95
3	4	50	IV	5	10	10.0
4	4	10	SC	1	10	10.0

Parameters[a]	2 mg/kg IV	10 mg/kg IV	50 mg/kg IV	10 mg/kg SC
n =	4	4	4	4
T_{max} (median)	18 min	33 min	5 min	3 days
C_{max} (µg/mL)	68 ± 6.2	290 ± 29	1400 ± 210	120 ± 13
C_0 (µg/mL)	66.7 ± 4.5	276 ± 18	1380 ± 170	131 ± 18
V_C/W (mL/kg)	30.1 ± 2.0	36.3 ± 2.4	36.8 ± 4.9	77.6 ± 11
V_{SS}/W (mL/kg)	64.0 ± 16	66.8 ± 8.3	73.9 ± 11	- b
CL/W (mL/day/kg)	4.76 ± 0.88	5.56 ± 0.46	5.78 ± 0.84	5.74 ± 0.85
$AUC_{5min-30\ days}$ (µg•day/mL)	369 ± 68	1620 ± 160	7760 ± 790	1520 ± 210
AUC (µg•day/mL)	430 ± 72	1810 ± 140	8800 ± 1400	1770 ± 260
$t_{1/2}$ absorption (hr)	-	-	-	18.5 ± 2.9
$t_{1/2}\alpha_1$ (hr)	11.5 ± 5.0	10.9 ± 2.4	19.2 ± 9.5	-
$t_{1/2}\alpha_2$ (day)	9.88 ± 1.9	8.75 ± 0.84	10.3 ± 3.1	9.39 ± 0.46
MRT (day)	13.4 ± 2.2	12.0 ± 1.0	13.1 ± 3.5	13.5 ± 0.66
Bioavailability (%)	-	-	-	98

a Reported as mean ± SD, unless otherwise noted.
b Not applicable.

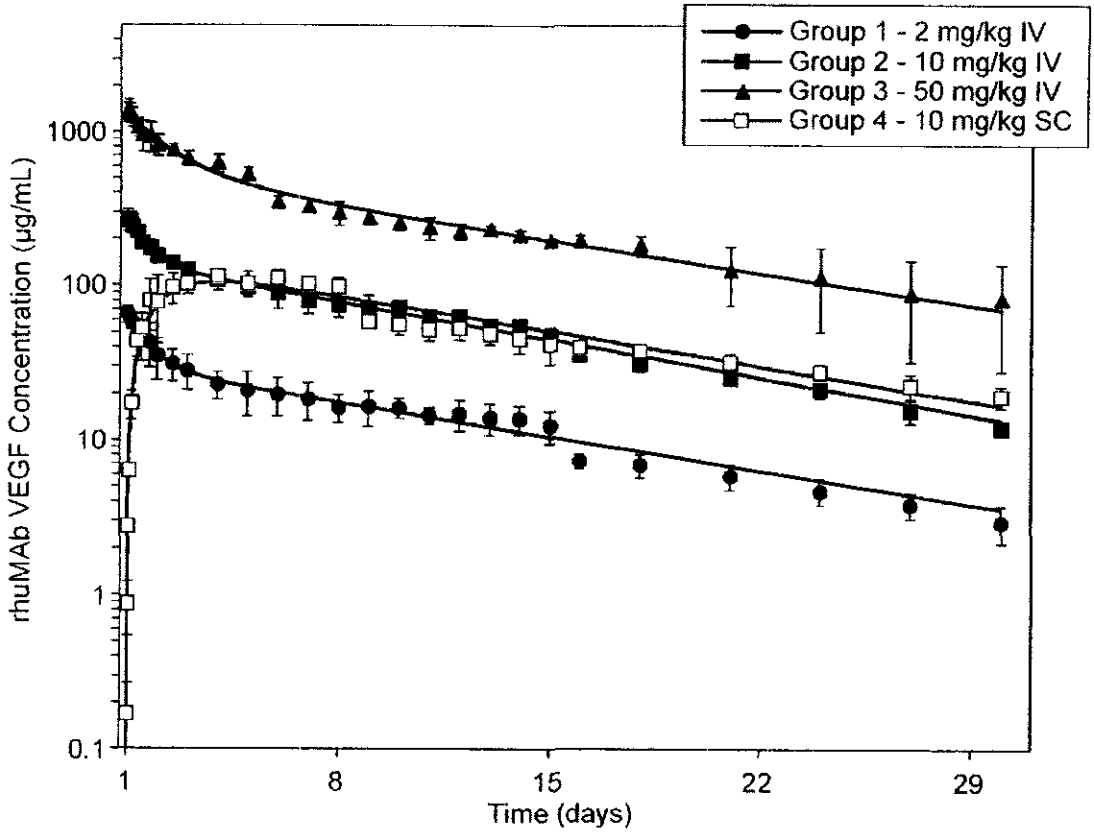

Figure 1. Serum concentration vs. time profiles of rhuMAb VEGF determined by ELISA with the mean fitted equation superimposed on the data. The mean ± SD of 4 monkeys for each group is presented.

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APPENDIX VI

Group	n=	Sacrifice Time	Specific Activity (μCi/μg)	^{125}I-labeled Dose (μCi/kg)	Protein Dose (μg/kg)
^{125}I-rhuMAb VEGF	2	2 hr	125	600	4.8
^{125}I-rhuMAb VEGF	2	48 hr	125	652	5.2
^{125}I-rhuMAb E25	2	2 hr	95	469	4.9
^{125}I-rhuMAb E25	2	48 hr	95	464	4.9

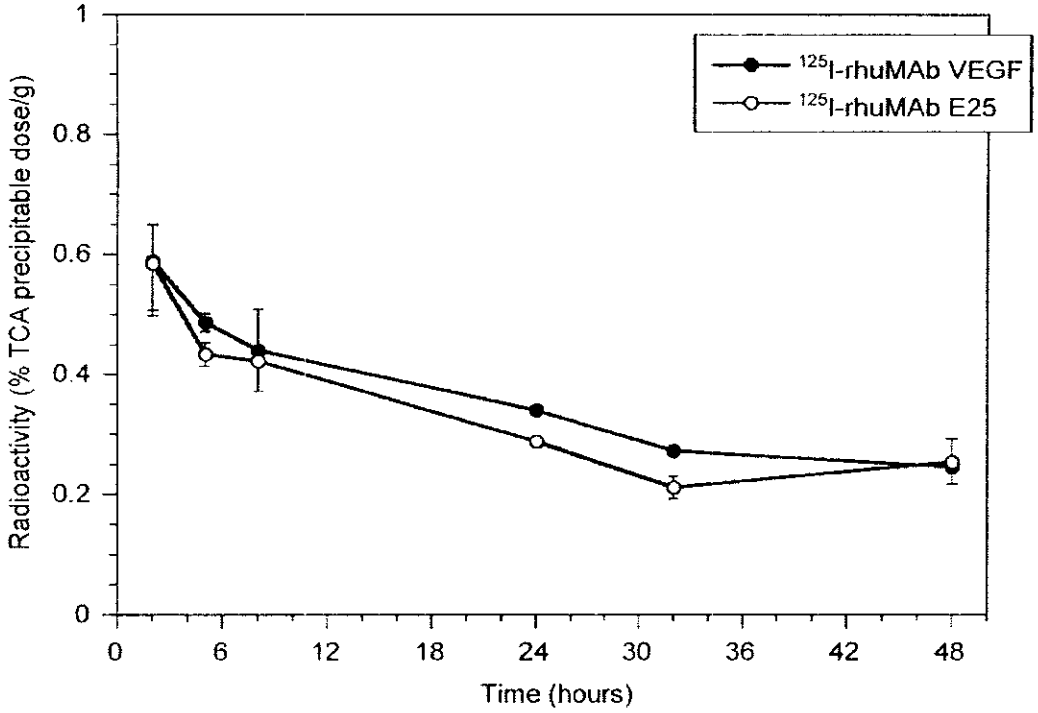

Figure 2. Plasma Concentration versus time profiles of ^{125}I-rhuMAb VEGF and ^{125}I-rhuMAb E25. At 2 hours, a mean of four animals per group is shown; at subsequent timepoints, a mean of two animals is shown per group - the error bars represent high and low values calculated for each group.

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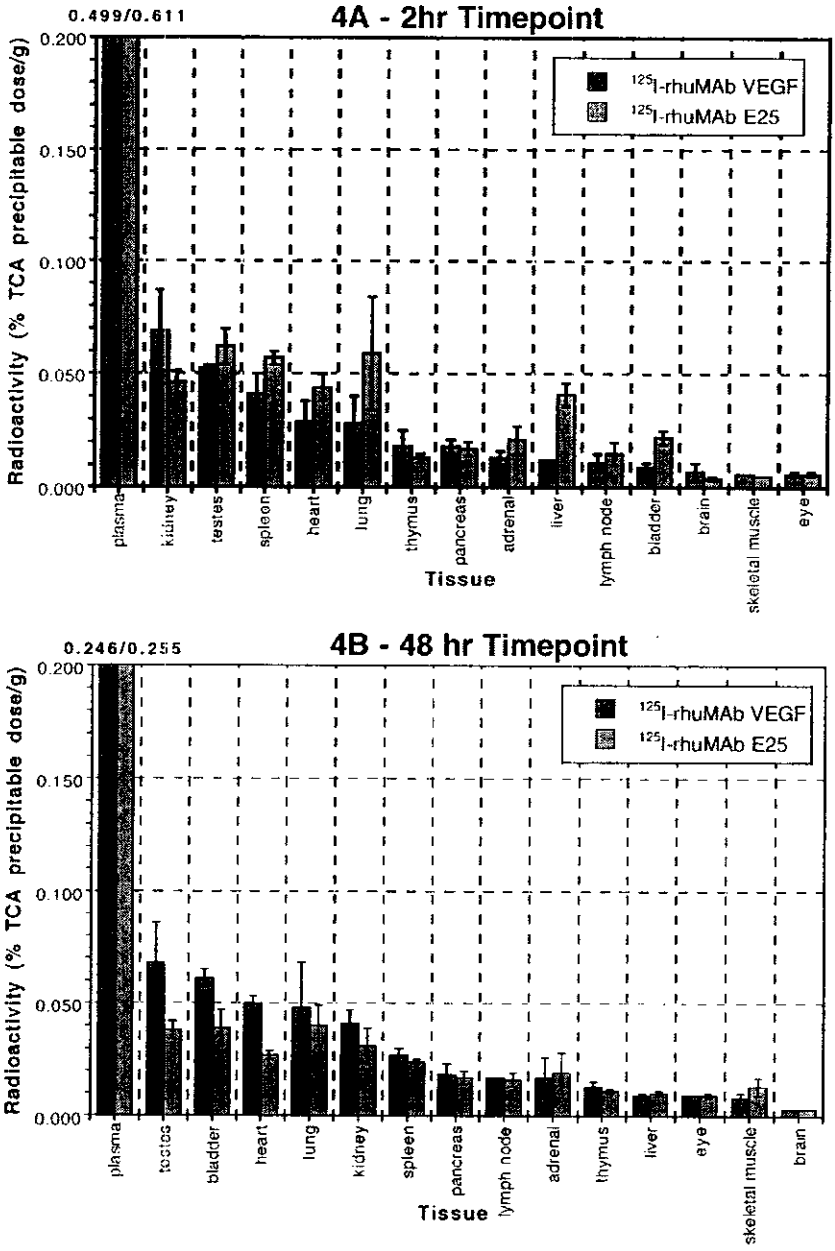
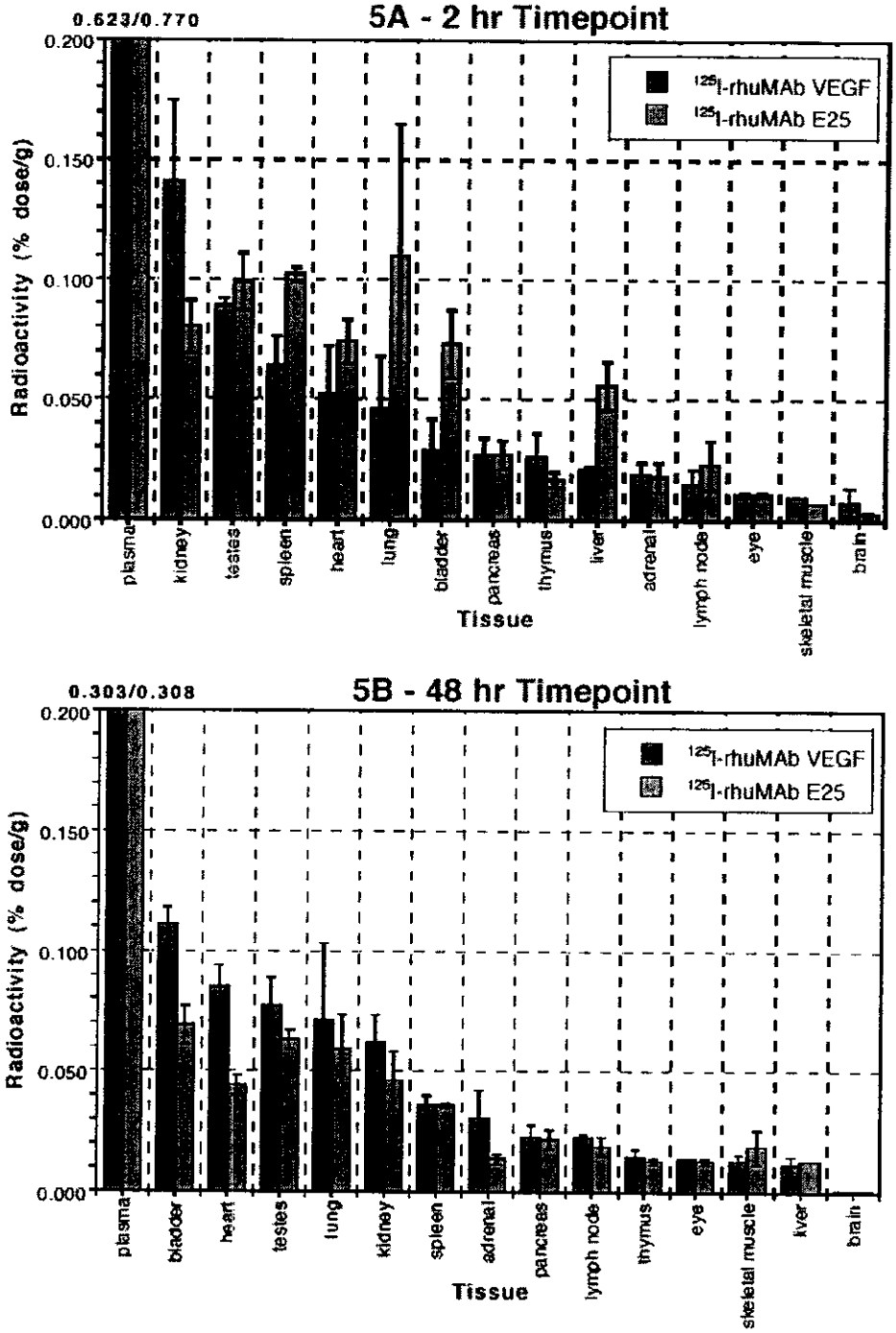


Figures 4A and 4B. Quantitation of TCA Precipitable Tissue Radioactivity of ^{125}I-rhuMAb VEGF and ^{125}I-rhuMAb E25 at 2 and 48 Hours Post-dose. Values are represented as % of TCA precipitable dose per gram of wet tissue. The error bars represent the individual values for the 2 animals in each group.



Figures 5A and 5B. Quantitation of Total Tissue Radioactivity of ^{125}I-rhuMAb VEGF and ^{125}I-rhuMAb E25 at 2 and 48 Hours Post-dose. Values are represented as % of administered dose per gram of wet tissue. The error bars represent the individual values for the 2 animals in each group.

APPENDIX VII

Group	Treatment	Dosing Days	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Males
1	rhuMAb VEGF Vehicle	1, 4, 8, 11, 15, and 18	0[a,b]	0	1.0	5
	saline	18	0[a,b]	0	1.0	
	saline	18	0[c]	0	3.3	
2	rhuMAb VEGF	1, 4, 8, 11, 15, and 18	10[a,b]	10	1.0	5
	saline	18	0[a,b]	0	1.0	
	saline	18	0[c]	0	3.3	
3	rhuMAb VEGF Vehicle	1, 4, 8, 11, 15, and 18	0[a,b]	0	1.0	5
	cisplatin	18	1[a,b]	1.0	1.0	
	Taxol®	18	4[c]	1.2	3.3	
4	rhuMAb VEGF	1, 4, 8, 11, 15, and 18	10[a,b]	10	1.0	5
	cisplatin	18	1[a,b]	1.0	1.0	
	Taxol®	18	4[c]	1.2	3.3	

a Administered as an intravenous bolus dose.
b The minicatheter was flushed with 3 mL of saline after dosing.
c Administered as a 1-hour infusion at a rate of 3.3 mL/kg/hour.

Table 2. Mean (± SD) rhuMAb VEGF Pharmacokinetic Parameters.

Parameters	Group 2 - rhuMAb VEGF	Group 4 - rhuMAb VEGF + cisplatin + Taxol®
T_{max} (median)	30 minutes	30 minutes
C_{max} (µg/mL)	676 ± 100	744 ± 120
V_c/W (mL/kg)	46.1 ± 10	37.1 ± 15
V_{ss}/W (mL/kg)	78.0 ± 8.4	72.5 ± 7.0
CL/W (mL/day/kg)	4.61 ± 1.3	3.99 ± 0.76
$t_{1/2\alpha_1}$ (hr)	28.6 ± 34	23.2 ± 14
$t_{1/2\alpha_2}$ (day)	13.5 ± 5.1	14.5 ± 2.7
MRT (day)	18.0 ± 6.0	18.5 ± 2.7
AUC (µg•day/mL)	2330 ± 740	2580 ± 510
AUC_1 (%)	7.43 ± 8.0	11.8 ± 9.0
AUC_2 (%)	92.6 ± 8.0	88.2 ± 9.0

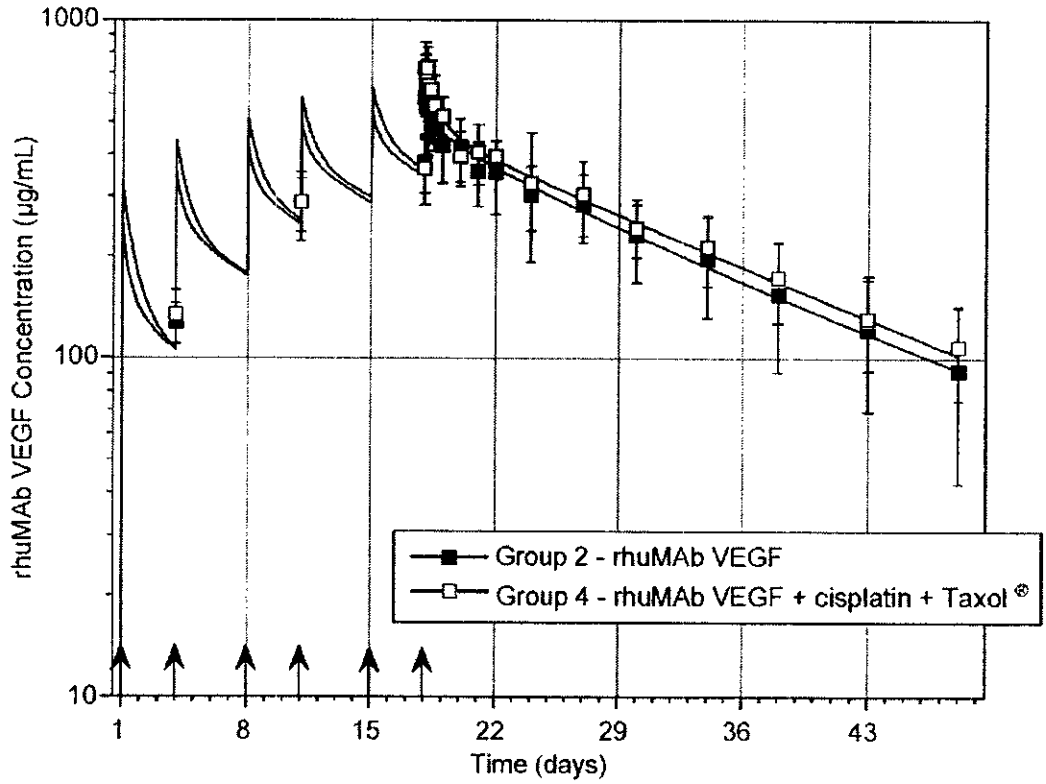


Figure 1. Mean (± SD) rhuMAb VEGF serum concentrations (µg/mL) after multiple administration of rhuMAb VEGF with the mean fitted equation superimposed on the data (n=5 per group).

Table 3. Mean (± SD) Cisplatin Pharmacokinetic Parameters.

Parameters	Group 3 - cisplatin + Taxol®	Group 4 - rhuMAb VEGF + cisplatin + Taxol®
T_{max} (median)	5 minutes	5 minutes
C_{max} (µg/mL)	5.01 ± 0.55	5.28 ± 0.50
C_0 (µg/mL)	5.99 ± 0.58	6.23 ± 0.69
V_c/W (mL/kg)	168 ± 17	162 ± 17
V_{ss}/W (mL/kg)	728 ± 160	637 ± 150
CL/W (mL/hr/kg)	10.8 ± 1.4	10.5 ± 2.3
$t_{1/2}\alpha_1$ (min)	13.4 ± 2.0	14.3 ± 2.4
$t_{1/2}\alpha_2$ (hr)	48.0 ± 11	43.4 ± 11
MRT (hr)	68.1 ± 16	61.6 ± 16
AUC_{tr} (µg•hr/mL)	60.0 ± 9.0	66.3 ± 14
AUC (µg•hr/mL)	94.1 ± 12	98.6 ± 19
AUC_1 (%)	1.59 ± 0.30	1.69 ± 0.54
AUC_2 (%)	98.4 ± 0.30	98.3 ± 0.54

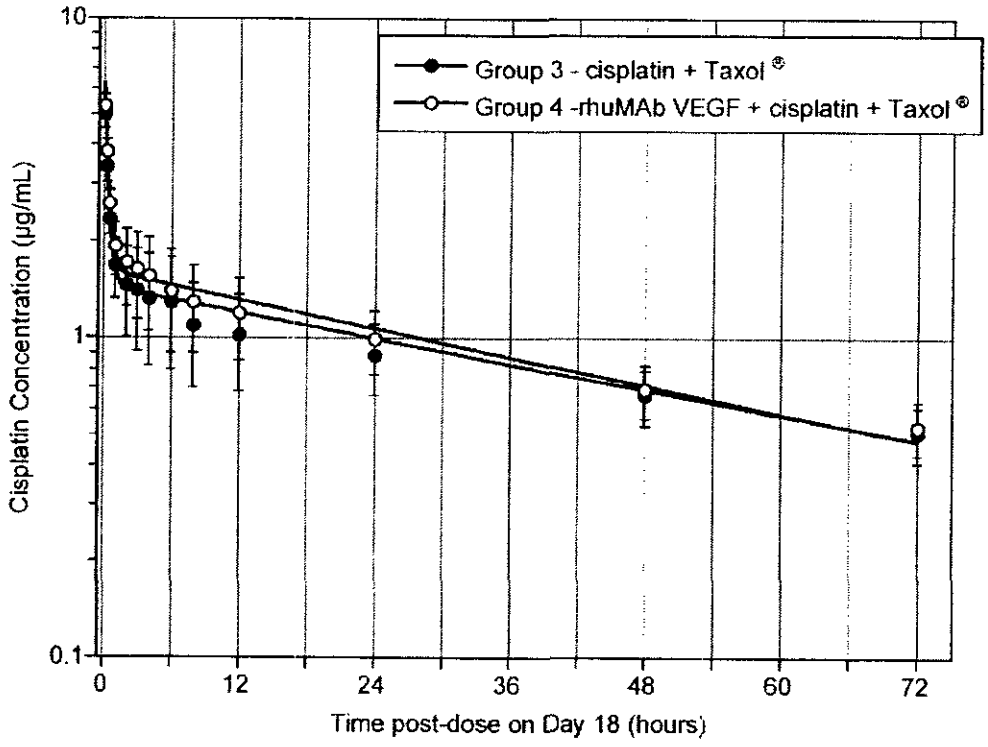


Figure 2. Mean (± SD) cisplatin plasma concentrations (µg/mL) after a single IV administration of cisplatin on Day 18 with the mean fitted equation superimposed on the data (n=5 per group).

Table 4. Mean (± SD) Taxol® Pharmacokinetic Parameters.

Parameters	Group 3 - cisplatin + Taxol®	Group 4 - rhuMAb VEGF + cisplatin + Taxol®
T_{max} (median)	1 hour	1 hour
C_{max} (µg/mL)	8.33 ± 2.9	8.73 ± 1.8
C_0 (µg/mL)	6.48 ± 2.2	6.86 ± 1.5
V_c/W (mL/kg)	343 ± 95	315 ± 56
V_{ss}/W (mL/kg)	1490 ± 590	1200 ± 220
CL/W (mL/hr/kg)	387 ± 130	357 ± 94
$t_{1/2}\alpha_1$ (min)	26.3 ± 1.6	27.3 ± 2.2
$t_{1/2}\alpha_2$ (hr)	7.55 ± 1.7	7.27 ± 1.4
MRT (hr)	3.92 ± 1.0	3.42 ± 0.45
AUC_{tr} (µg•hr/mL)	10.3 ± 3.7	10.9 ± 2.9
AUC (µg•hr/mL)	11.5 ± 4.3	12.0 ± 3.7
AUC_1 (%)	68.2 ± 4.1	71.2 ± 5.9
AUC_2 (%)	31.8 ± 4.1	28.8 ± 5.9

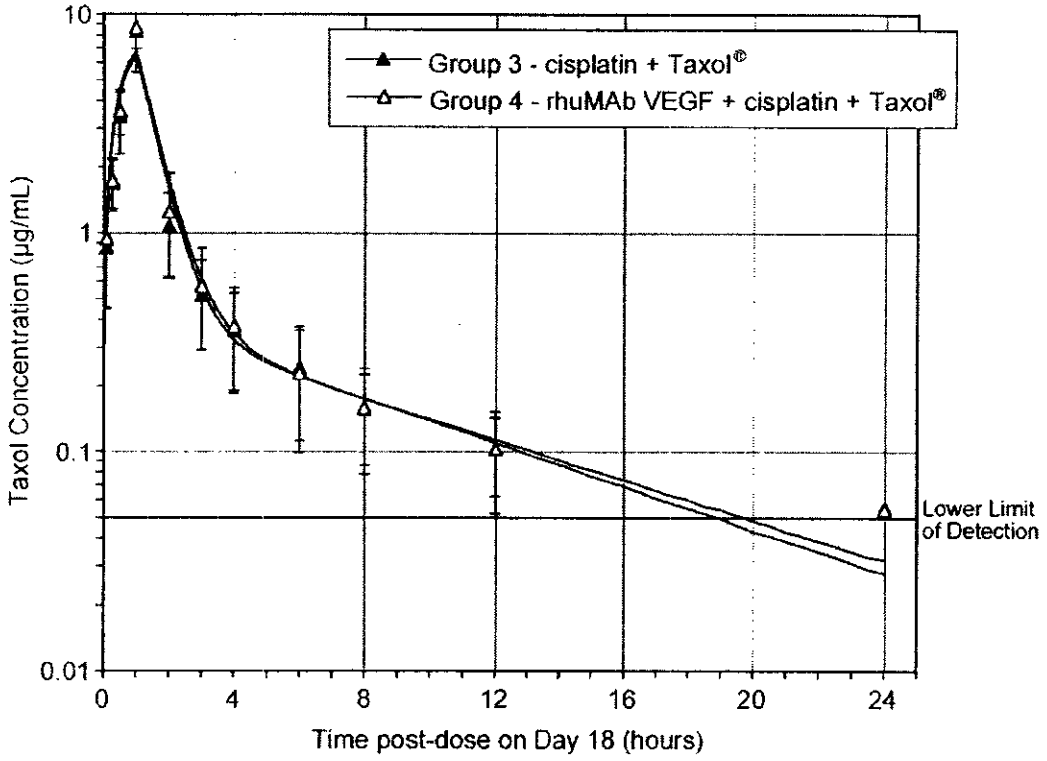


Figure 3. Mean (± SD) Taxol® plasma concentrations (µg/mL) following IV infusion of Taxol® on Day 18 with mean fitted equation superimposed on the data (n=5 per group).

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APPENDIX VIII

		CPT-11		LV		5-FU		rhuMAb VEGF	
Group	No. of Males	Dose (mg/m^2)	Conc. (mg/mL)	Dose (mg/m^2)	Conc. (mg/mL)	Dose (mg/m^2)	Conc. (mg/mL)	Dose (mg/kg)	Conc. (mg/mL)
1	4	125	1	20	20	500	50	0	0
2	5	125	1	20	20	500	50	10	10
3	3	100	0.8	20	20	500	50	0	0

The dose and dose volumes for CPT-11, LV, and 5-FU were based on body surface area and adjusted for each animal according to the following relationship:
Body surface area (m^2) = [body weight (g)$^{0.667}$ x 11.8]/ 10,000.
The dose volume for rhuMAb VEGF was 1 mL/kg.
Day 1 for Group 1 was 29 August 2000.
Day 1 for Group 2 was 05 September 2000.
Day 1 for Group 3 was 19 September 2000.
Day 1 for additional Group 1 and 2 animals was 10 October 2000.

Figure 1
Mean Plasma CPT-11 Concentrations following Intravenous Administration of CPT-11/5-FU/LV with (Group 2) or without (Groups 1 and 3) rhuMAb VEGF at Days 1 and 8

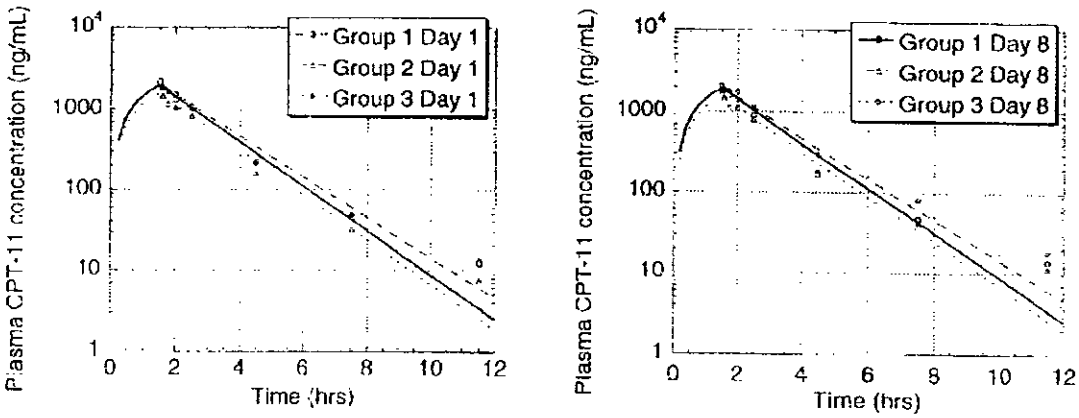

Table 3
Mean (±SD) Plasma CPT-11 Pharmacokinetic Parameters following Administration of CPT-11/ 5-FU/LV with (Group 2) or without (Groups 1 and 3) rhuMAb VEGF on Days 1 and 8

	Group [n] (treatment)		
Parameter	1 [4] (CPT-11 125/5-FU/LV)	2 [5] (CPT-11 125/5-FU/LV/ rhuMAb VEGF)	3 [3] (CPT-11 100/5-FU/LV)
CL ($L/hr/m^2$)	26.9 (2.86)	25.0 (4.72)	27.6 (5.43)
V_{ss} (L/m^2)	42.0 (4.57)	42.7 (9.47)	42.8 (7.59)
$t_{1/2}$ (hr)	1.09 (0.0666)	1.18 (0.124)	1.08 (0.0363)
C_{max} (µg/mL)	1.93 (0.203)	2.01 (0.432)	1.54 (0.314)
AUC_{inf} (ng/mL • hr)	4700 (514)	5150 (1050)	3730 (806)

Figure 2

Mean Plasma 5-FU Concentrations following Intravenous Administration of CPT-11/ 5-FU/LV with (Group 2) or without (Groups 1 and 3) rhuMAb VEGF on Days 1 and 8

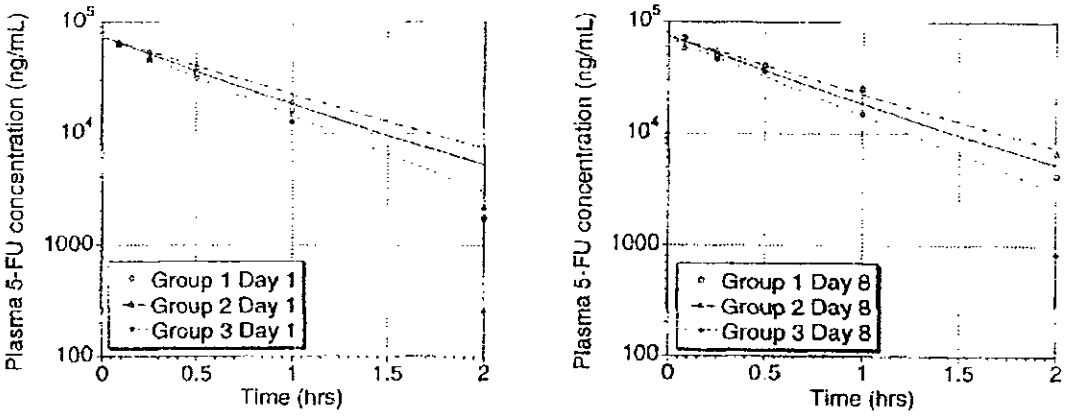

Table 4

Mean (±SD) Plasma 5-FU PK Parameters following Administration of CPT-11/5-FU/LV with (Group 2) or without rhuMAb VEGF (Groups 1 and 3)

	Group [n] (treatment)		
Parameters	1 [4] (CPT-11 125/5-FU/LV)	2 [5] (CPT-11 125/5-FU/LV/ rhuMAb VEGF)	3 [3] (CPT-11 100/5-FU/LV)
CL (L/hr/m^2)	9.72 (2.49)	8.33 (2.30)	11.4 (1.47)
V_{ss} (L/m^2)	6.77 (0.553)	6.86 (0.849)	7.05 (0.158)
$t_{1/2}$ (hr)	0.515 (0.174)	0.600 (0.154)	0.434 (0.0584)
AUC_{inf} (ng/mL • hr)	54400 (15700)	63400 (15400)	44400 (6190)

APPEARS THIS WAY
ON ORIGINAL