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BLA APPLICATION NUMBER:

125156

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BLA#	BL 125156-0.000, BL 125156-0.011
PRODUCT	Ranibizumab (Lucentis®)
FORMULATION	Liquid single use vial for intravitreal injection
SUBMISSION DATES	December 29, 2005; May 5, 2006
SUBMISSION TYPE	Biologic License Application
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CLINICAL PHARMACOLOGY REVIEW

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1 EXECUTIVE SUMMARY

Ranibizumab (rhuFab V2) is a recombinant, humanized antibody antigen-binding fragment (Fab) that binds to and neutralizes vascular endothelial growth factor-A (VEGF-A). VEGF promotes the formation of new blood vessels. VEGF is secreted from ischemic tissues and from malignant cells and binds to two high-affinity tyrosine kinase receptors on endothelial cells, VEGFR-1 and VEGFR-2, causing vascular leakage and new blood vessels to form locally. The maximal inhibition of rhVEGF-induced proliferation of human umbilical vein endothelial cells (HUVEC) was observed at ranibizumab concentrations of approximately 1.29 nM (which is equivalent to 62 ng/mL, assuming a molecular weight for ranibizumab of 48kDa). In the same assay, the concentration range of ranibizumab needed to reduce VEGF-induced endothelial cell proliferation by 50% (IC_{50}) was 0.23- 0.56 nM, which is equivalent to 11-27 ng/mL.

VEGF is an endothelial cell-specific mitogen and survival factor as well as a regulator and promoter of angiogenesis during developmental, physiological, and pathological processes. Endothelial cells that are present in choroidal neovascular membrane are strongly dependent on VEGF for cell survival and interference with VEGF activity induces endothelial apoptosis. It is this difference between normal and choroidal neovascularization (CNV)-associated vasculature with respect to VEGF dependence by endothelial cells for survival that support the rationale for clinical use of an anti-VEGF Fab as a therapeutic agent to treat patients with age-related macular degeneration (AMD).

The observed ranibizumab serum concentrations following intravitreal injection are generally low (less than 3 ng/mL) and increase proportionately with dose over the 0.05 to 1 mg/eye ranibizumab dose range. Utilizing the data collected from 5 clinical studies (Phase I, II and III studies), a population PK model was developed by the Sponsor; and the model predicted steady-state minimum vitreous concentration was 20 µg/mL (5^{th}-95^{th} percentile range: 3.8-68 µg/mL) for 0.5 mg/eye ranibizumab dose. The predicted maximum steady-state serum ranibizumab concentration was 1.5 ng/mL (5^{th}-95^{th} percentile range: 0.79 -2.9 ng/mL) for the 0.5 mg/eye dose. These predicted concentrations support low systemic exposure to ranibizumab and hence, relatively low effect on VEGF-A systemic activity and vitreous concentrations that are significantly higher than the concentrations necessary to completely inhibit ocular VEGF-A activity (as determined by in vitro assays).

This application contains seven trials that have included the investigation of the pharmacokinetics (five trials) and pharmacodynamics (seven trials) of ranibizumab (dosing range of 0.05mg to 2mg) in humans. The clinical results show that intravitreal administration of 0.5mg ranibizumab monthly in diagnosed AMD patients will cause an increase in visual acuity, a decrease in leakage from CNV, and a reduction in retinal thickness.

1.1 Recommendations

This biologic license application is acceptable from a Clinical Pharmacology standpoint.

1.2 Phase 4 Commitments
There are no phase 4 commitments.

1.3 Summary of Important Clinical Pharmacology Findings
Pharmacokinetic and pharmacodynamic data for ranibizumab are available from six clinical studies, in which ranibizumab was administered either as a single agent or in combination with verteporfin PDT to subjects with neovascular AMD.

Pharmacokinetics:

Ranibizumab is administered intravitreally for the treatment of neovascular AMD and subsequently slowly absorbed into the systemic circulation. The elimination of ranibizumab from the systemic circulation is believed to be absorption rate limited based on nonclinical PK data. In the noncompartmental PK analysis of serum concentration data from ten subjects in the Phase I study FVF1770g, ranibizumab serum concentration versus time profiles were observed to decline monoexponentially and ranibizumab area under the concentration-time curve (AUC) increased in a dose-proportional manner, which suggested linear PK over the dose range studied. The results from these ten subjects also indicated that ranibizumab serum concentrations following a single intravitreal ranibizumab dose of 0.3-1.0 mg/eye, were less than 3 ng/mL and as indicated above, lower than the concentration range of ranibizumab needed to reduce VEGF-induced endothelial cell proliferation by 50% (IC_{50}); 0.23- 0.56 nM, which is equivalent to 11-27 ng/mL.

A population PK approach was followed to analyze the data obtained from five ranibizumab clinical studies (FVF1770g, FVF2425g, FVF2128g, FVF2428g, and FVF2598g). In four of those studies ranibizumab was used as a single agent and in one study ranibizumab was administered to subjects concomitantly with verteporfin PDT. The analysis included a total of 675 measurable samples of ranibizumab from 228 subjects who received doses of ranibizumab, ranging from 0.05 to 2.0 mg/eye, either as a single dose or in a multiple dose regimen at a frequency ranging from every two weeks to every month. In all of these studies ranibizumab was administered intravitreally as a bolus to one study eye. Based on the final model, several covariates were correlated with population PK parameter estimates. Serum creatinine clearance (CrCL) was found to be the most significant covariate for apparent systemic clearance (CL/F) of ranibizumab. However, given the large intersubject variability of CL/F, the contribution of the component related to creatinine clearance and hence renal elimination of ranibizumab to the overall clearance of ranibizumab is relatively small. While a specific renal impairment study was not conducted, data from the clinical studies was utilized to assess the effect of renal impairment on ranibizumab apparent clearance. In the pooled data for the POP PK analysis, 68% (136 of 200) patients had renal impairment (i.e. of the 200 patients, the percentage of patients with mild, moderate and severe renal impairment were 45.5%, 20%, and 1.5%, respectively). Based on the POP PK model, renal impairment is not likely to result in a significant increase in ranibizumab exposure, so an increase in

exposure due to renal impairment would be minimal and is considered to be of no clinical significance. Ranibizumab dose adjustment is not needed in patients with renal impairment.

In population PK analysis, after correcting for creatinine clearance, age did not have a significant effect on ranibizumab exposure.

For a typical subject, the apparent clearance of ranibizumab was 24.4 L/day, the apparent volume of the central compartment was 3.22 L, the elimination rate of ranibizumab was 0.0700 day^{-1} and its elimination half life was approximately nine days. Based upon the results of the Population PK analysis, there is no covariate that affects the systemic exposure of ranibizumab with clinical significance.

Pharmacodynamics:

In vivo, neovascular AMD is associated with foveal thickness as assessed by optical coherence tomography (OCT) and leakage from CNV as assessed by fluorescein angiography.

The pharmacodynamics of ranibizumab in humans with neovascular AMD was evaluated using OCT and fluorescein angiography. In the two phase 3 studies, patients treated with ranibizumab (pooled data from the 0.3mg and 0.5mg groups), on average, foveal thickness decreased by Day 7 and continued to decrease through Month 12. At Month 12, the average change in Study FVF2598g was -123 μm for ranibizumab compared with -15μm for sham-injection control ($p=0.009$). In Study FVF2587g, the average change was -190 μm for ranibizumab compared with -87μm for vertoporfin PDT ($p=0.0004$). In subjects treated with monthly injections of ranibizumab in both phase 3 studies, the area of leakage from CNV as assessed by fluorescein angiography decreased by Month 3. In Study FVF2598g, the average change was approximately -1.0 disc areas (DA) for subjects in both the 0.3mg and 0.5mg ranibizumab groups versus +0.8 DA for those in the sham-injection control group ($p<0.0001$). In Study FVF2587g, it was approximately -1.3 DA for subjects in both the 0.3mg and 0.5mg ranibizumab groups compared with +0.2 DA for subjects in the verteporfin PDT group ($p<0.0001$).

These results are consistent with the predicted high vitreous concentrations of ranibizumab and its expected ocular anti-VEGF activity.

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cc:
Division File: BLA 125156
HFD-520 (CSO/Gorski)
HFD-520 (MO/Lloyd)
HFD-880 (Division File, Lazor, Selen, Jarugula, Tworzyanski)
CDR (Clin. Pharm.)

2 QUESTION-BASED REVIEW
2.1 General Attributes of ranibizumab

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug products?

Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment specifically designed for intraocular use. Ranibizumab has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product. Ranibizumab is supplied as a sterile, colorless to pale yellow solution in a single-use glass vial for intravitreal injection. Particulate specifications meet those required by USP for opthlamic use. Each single-use vial is designed to deliver 0.05ml of 10mg/ml ranibizumab aqueous solution with 10 mM histidine HCL, 10% α-trehalose dehydrate, 0.01% polysorbate 20, pH 5.5.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ranibizumab binds with high affinity to the receptor binding site for all known forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in ocular angiogenesis, both of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration (AMD), a leading cause of blindness. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of the endothelial cells. The interaction of VEGF-A binding to its receptor leads to endothelial cell proliferation, vascular leakage, and new blood vessel formation.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose of Lucentis® is 0.5mg (0.05mL) administered by intravitreal injection once a month.

2.2 General Clinical Pharmacology
2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

This application contains seven trials that have included the investigation of the pharmacokinetics (five trials) and pharmacodynamics (seven trials) of ranibizumab (dosing range of 0.05mg to 2mg) in humans. In all of the clinical trials, ranibizumab was administered to subjects as an intravitreal bolus injection. All studies were conducted in subjects with neovascular AMD. Table 1 shows the doses, dosing frequency and the sampling scheme from most of these studies.

Table 1.

Summary of Studies of Ranibizumab Providing Pharmacokinetic or Pharmacodynamic Data

Phase	Study; Indication	Dose (mg/eye)	Frequency	Concomitant Medications	Sampling Scheme Frequency
I	FVF1770g; neovascular AMD	0.05, 0.15, 0.3, 0.5, and 1.0	Single dose	None	Serial samples collected through Day 90 for all subjects
	FVF2425g; neovascular AMD	0.3, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, and 2.0	Intra-subject dose escalation, every 2 weeks or every 4 weeks	None	Multiple peaks and troughs for all subjects
I/II	FVF2128g; neovascular AMD	0.3 and 0.5	Every 4 weeks for 4 or 8 doses	None	Multiple peaks and troughs, plus Day 14, 42, and 98 samples from all subjects
	FVF2428g;[a] predominantly classic, neovascular AMD	0.5	Monthly for 24 months	Verteporfin PDT	Day 7 and 14 samples after the first ranibizumab injection and multiple troughs for all subjects
III	FVF2598g;[a] minimally classic or occult, neovascular AMD	0.3 and 0.5	Monthly for 24 months	None	Trough concentrations at Months 6, 12, and 24
	FVF2587g;[a] predominantly classic, neovascular AMD	0.3 and 0.5	Monthly for 24 months	None	Trough concentrations at Months 6, 12, and 24

AMD=age-related macular degeneration; PDT=photodynamic therapy.

[a] Samples of vitreous fluid were obtained if a subject underwent a medically necessary vitrectomy.

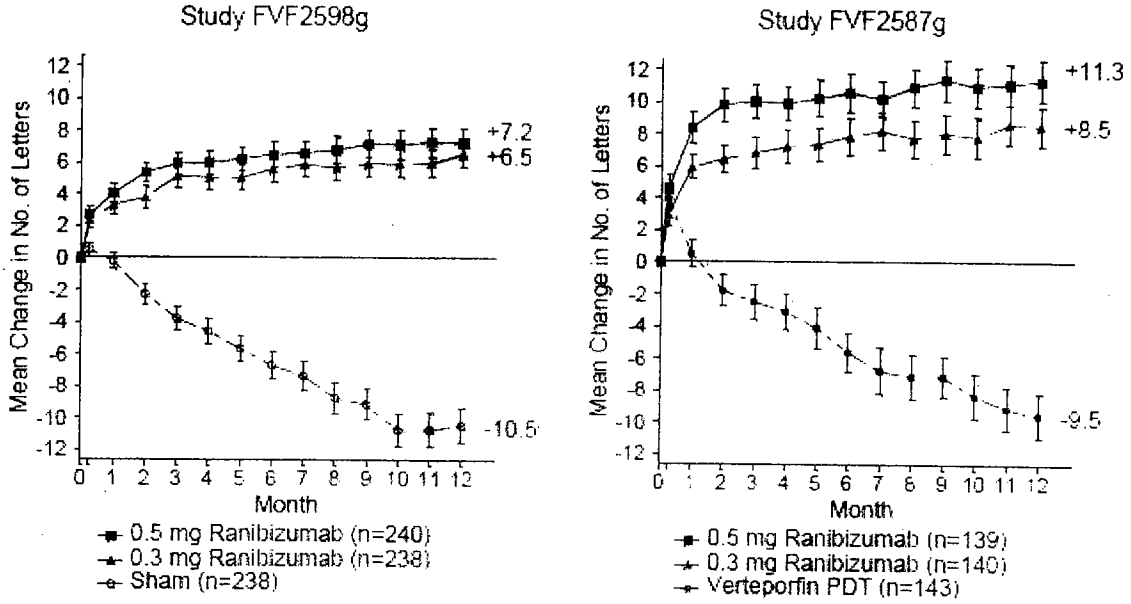
2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationship for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

There seems to be clinical benefit of both 0.3mg and 0.5mg ranibizumab administered monthly intravitreally over 12 months to subjects with neovascular AMD. Please see Dr. Rhea Lloyds' review for a detailed description and analyses of efficacy and safety data. Clinically meaningful and statistically significant visual acuity benefits were seen at 1 year for both doses across all CNV lesion types in the phase III studies FVF2598g and FVF2587g. Improvement was seen for the primary endpoint of the proportion of subjects losing <15 letters as well as for the secondary visual acuity endpoints of the proportion of subjects gaining ≥15letters at 12 months, the mean change from baseline over time in visual acuity score (as displayed in Figure 1), and the proportion of subjects with a Snellen equivalent visual acuity of 20/200 or worse.

Figure 1.

Mean Change from Baseline over Time up to 12 Months in Visual Acuity: Randomized Subjects in Studies FVF2598g and FVF2587g



Note: Vertical bars are ± 1 standard error of the mean. The assessments conducted at a starting test distance of 2 meters were used. Missing data were imputed using the LOCF method.

Results from Phase III studies FVF2598g and FVF2587g show monthly doses of 0.3mg and 0.5mg ranibizumab administered to subjects by intravitreal injection are equally effective in maintaining vision, defined as losing <15 letters of best-corrected visual acuity at 12 months. With regard to the secondary efficacy endpoints, both doses of ranibizumab showed a substantial benefit compared with control. There appears to be slightly better outcomes for subjects receiving 0.5mg ranibizumab compared with 0.3mg ranibizumab in the secondary endpoints of the proportion of subject gaining ≥15 letters and the mean change in visual acuity score at baseline at 12 months. No formal statistical comparisons were performed to compare the outcomes of the ranibizumab dose.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The ocular safety profile was favorable in studies FVF2598g and FVF2587g. Key serious ocular adverse events of endopthalmitis, serious intraocular inflammation, retinal detachment, retinal tear, increased intraocular pressure (IOP), and traumatic cataract were all common in ranibizumab-treated subjects (reported <1% of subjects for each event. Per injection rates for the serious adverse events of endophthalmitis, intraocular inflammation, retinal detachment, and traumatic cataract were all very low (≤0.12% per injection in each dose group) in Studies FVF2598g and FVF2587g. the most common study eye

ocular adverse events in these two studies reported more often in the ranibizumab groups than in the control groups appear to be largely related to the conjunctival anesthetic and intravitreal injection procedures. Among the two treatment groups in Studies FVF2598g and FVF2587g, there was no imbalance in the overall incidence of adverse events potentially related to systemic VEGF inhibition. Table 2 displays adverse events.

Table 2.

Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year: Studies FVF2598g and FVF2587g

	Study FVF2598g			Study FVF2587g		
		Ranibizumab			Ranibizumab	
Event	Sham (n=236)	0.3 mg (n=238)	0.5 mg (n=239)	Verteporfin PDT (n=143)	0.3 mg (n=137)	0.5 mg (n=140)
Adverse events	47 (19.9%)	44 (18.5%)	42 (17.6%)	22 (15.4%)	17 (12.4%)	29 (20.7%)
Serious adverse events	2 (0.8%)	8 (3.4%)	9 (3.8%)	3 (2.1%)	4 (2.9%)	8 (5.7%)
APTC arterial[a] thromboembolic events	2 (0.8%)	3 (1.3%)	5 (2.1%)	3 (2.1%)	3 (2.2%)	6 (4.3%)

[a] Arterial thromboembolic events, defined according to the Antiplatelet Trialists' Collaboration classification (1994), are presented.

A small trend in the incidence of serious adverse events potentially related to systemic VEGF inhibition was observed for the ranibizumab groups, reflecting trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria). Please see Dr. Rhea Lloyds' review for more information. Using the more objective APTC classification (Antiplatelet Trialists Collaboration 1994), a small increase in the overall trend in serious arterial thromboembolic events was observed in subjects treated with monthly 0.5mg ranibizumab compared with other subjects.

2.2.5.3 What are the characteristics of drug absorption?

Ranibizumab is administered by intravitreal injection.

The sponsor observed that this drug exhibited "flip-flop" kinetic characteristics. The systemic elimination half-life was estimated to be 0.09 days (two hours), whereas the vitreous elimination half-life was estimated to be approximately nine days based on preclinical data. Because the rate of vitreous elimination is the rate-limiting step, the apparent half-life of ranibizumab in serum after ITV administration is equivalent to the vitreous elimination half-life, which is approximately nine days.

Table 3 shows the mean PK parameters for subjects across all studies. Considering the intravitreal route of administration for ranibizumab and the limited absorption into the systemic circulation, systemic PK data are sparse and low in concentration. The systemic PK of ranibizumab was characterized by a population analysis, since each study did not provide sufficient information for individual estimation of PK parameters. As is shown in Table 3, the typical apparent central compartment volume of distribution of ranibizumab is 3.22 L.

Table 3.

Mean and Coefficient of Variation of Pharmacokinetic Parameters and Covariates by Study

Parameter	Study					All Studies
	FVF1770g	FVF2128g	FVF2425g	FVF2428g	FVF2598g	
No. of subjects with ≥1 measurable serum concentration	24	57	29	98	30	238
No. of subjects with ≥1 evaluable serum concentration [a]	24	54	29	97	24	228
CL/*F* (L/day)	23.3 (25)	23.6 (21)	25.3 (26)	25.2 (21)	23.1 (17)	24.4 (22)
V_c/F (L)	2.88 (33)	3.10 (52)	4.55 (60)	2.99 (4)	3.15 (25)	3.22 (43)
K_a (day^{-1})	0.0861 (18)	0.0807 (15)	0.0880 (20)	0.0515 (13)	0.0783 (13)	0.0698 (28)
CrCL (mL/mim)	67 (30)	63 (30)	57 (38)	79 (37)	65 (0) [c]	70 (35)
PDT (0/1) [b]	23/1	55/2	29/0	0/98	30/0	137/101

CL/*F*=apparent systemic clearance; CrCL=serum creatinine clearance; K_a=rate of systemic absorption (rate of vitreous elimination); PDT=photodynamic therapy; V_c/F=apparent central compartment volume of distribution.

[a] A subject could have had all of his or her measurable serum sample(s) excluded from the analysis as an outlier(s) and become unevaluable.

[b] PDT=0: subject never received PDT during screening or treatment; PDT=1: subject received at least one PDT treatment during screening or the study period.

[c] CrCL for the 30 subjects with measurable serum concentration was imputed to the population median because body weight was not recorded in Study FVF2598g.

2.2.5.4 What are the characteristics of drug distribution?

Based on a population PK analysis, maximum serum concentrations of 0.91 ng/ml are predicted to be reached on Day 1 with monthly intravitreal administration of ranibizumab 0.3mg/eye, and 1.5 ng/ml after administration of 0.5 mg/eye. Based on the disappearance of ranibizumab from the serum, the estimated average vitreous elimination half-life was approximately nine to ten days. Steady-state minimum concentration is predicted to be 0.13 ng/ml with a monthly dosing regimen for the 0.3 mg dose and 0.22 ng/ml for the 0.5 mg dose. In humans, the ratio of ranibizumab concentrations in serum to vitreous humor is estimated as 1/90,000 after the 0.3 mg dose and 1/140,000 after the 0.5mg dose.

2.2.5.5 Does the mass balance study suggest renal, or hepatic as the major route of elimination?

The mass balance study for ranibizumab has not been conducted.

2.2.5.6 What are the characteristics of drug metabolism?

Ranibizumab is not metabolized but degradated.

2.2.5.7 What are the characteristics of drug excretion?

Intact ranibizumab is not known to be excreted, however, it is likely that its fragments are excreted by the kidneys.(The role of the kidney in the catabolism of Bence Jones proteins and immunoglobulin fragments by Wochner RD, Strober W, Waldmann TA in J. Exp. Med 1967; 126(2):207-21).

2.2.6 Immunogenicity

The sponsor reported a pre-treatment incidence of immunoreactivity to ranibizumab as 0-3% across the treatment groups. After 12 months of treatment with ranibizumab, low titers of antibodies to ranibizumab were detected in approximately 1-4% of patients. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to ranibizumab in an electrochemiluminescent assay (ECLA). These results are highly dependent on several factors including the sensitivity and specificity of the assay, sample handling, timing of sample collection, and underlying disease.

2.3 Intrinsic Factors
2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, what dosage regimen adjustments, if any are recommended for each of these groups?

2.3.2 Elderly

In studies FVF2598g and FVF2587g approximately 93% (706/758) of the patients randomized to treatment with ranibizumab were ≥65 years of age and approximately 67% (509/758) were ≥75 years of age. No notable difference in treatment effect was seen with increasing age in either study. In the population PK analysis, after correcting for creatinine clearance, age did not have significant effect on systemic exposure.

2.3.2.2 Pediatric Patients

The safety and effectiveness of ranibizumab in pediatric patients has not been studied.

2.3.2.5 Renal Impairment

Dose adjustment is not needed for patients with renal impairment. No formal studies have been conducted to examine the PK of ranibizumab in patients with renal impairment. Sixty-eight percent of patients (136 of 200) in a population PK analysis had renal impairment (46.5% mild, 20% moderate, and 1.5% severe). Clearance of ranibizumab from the systemic circulation was slightly lower in these patients, but it was not clinically significant. Table 4 shows the estimated ranibizumab creatinine clearance values based on pharmacometric modeling.

Table 4. Individual Post Hoc CL per Renal Function Groups

Renal Function [a]	Estimated CrCL (mL/min)	No. of Subjects (% of Total)	Ranibizumab CL Mean ± SD (L/day)
Normal	>80	64 (32.0)	27.0 (5.2)
Mild impairment	50–80	93 (46.5)	24.2 (5.0)
Moderate impairment	30–50	40 (20.0)	22.3 (5.7)
Severe impairment	<30	3 (1.5)	15.7 (1.6)

[a] Renal function was grouped per FDA guidance (FDA Guidance for Industry 1998).

Although there is no need for dose adjustment, there may be a concern for patients with severe renal impairment if the formulation and/or dosing regimen changes.

2.3.2.6 Hepatic Impairment

No formal studies have been conducted to examine the PK of ranibizumab in patients with hepatic impairment.

2.3.2.7 What pregnancy and lactation use information is there in the application?

No studies assessing the potential of intravitreal administration of ranibizumab to cause teratogenicity have been conducted. Ranibizumab should not be used during pregnancy or by any woman not employing adequate contraception only if the potential benefit justifies the potential risk to the fetus. It is not known whether ranibizumab is excreted in human milk.

2.4.1 What extrinsic factors (drug, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

Drug interaction studies have not been conducted with ranibizumab.

2.6 Analytical section

2.6.4.1 What bioanalytical methods are used to assess concentrations?

Ranibizumab was measured by electrochemiluminescence assay (ECLA). Serum ranibizumab (rhuFab V2) were determined by ECLA using

This assay measured ranibizumab in human serum. Concentrations of <0.3 ng/ml were considered less than reportable (below the limit of quantification). Plasma VEGF concentrations were determined by an ELISA assay using a combination of murine monoclonal anti-rhVEGF and affinity

A urine monoclonal anti- rhVEGF antibody

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✓ § 552(b)(4) Draft Labeling

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4.2 Clinical pharmacology and biopharmaceutics individual study review

Study FVF1770g

A Phase I, open-label, multicenter study of five escalating doses (0.05, 0.15. 0.3, 0.5, and 1.0mg) of ranibizumab administered to subjects as a single intravitreal injection. The study objectives were to investigate the ocular and systemic safety and tolerability of ranibizumab administered as a single intravitreal injection, to characterize the PK of serum ranibizumab and plasma VEGF concentrations over time following a single intravitreal injection of ranibizumab, and to explore the activity of ranibizumab on new vessels, as assessed by visual acuity and angiography. Serum ranibizumab concentrations were reported at the Day 1 and Day 7 timepoints for a given subject (n=15) or was reported at the Day 1, Day 7, and Day 14 timepoints for a given subject (n=10).

Serum ranibizumab concentrations ranged from 0.304-2.94 ng/ml. These measurable results were below the ranibizumab concentration expected to impact VEGF-mediated activity (~ 10ng/mL).With increasing dose the overall exposure increases, as well as the maximally observed mean concentration per dose group. The maximum observed serum concentration was dose proportional over the dose range of 0.05-1.0 mg/eye. Mean estimates of exposure, area under the concentration-time curve measured from Time 0 to the last quantifiable timepoint, Day 7 or Day 14 ($AUC_{0\text{-}D7}$ or $AUC_{0\text{-}D14}$), are shown in Table 7.

Table 7

Noncompartmental Estimates of Ranibizumab Systemic Exposure, AUC_{0-D7}, AUC_{0-D14}: Study FVF1770g

Dose (mg)	n	AUC_{0-D7} (day • pg/mL) [a]	n	AUC_{0-D14} (day • pg/mL) [a]
0.15	2	(3460, 4850) [b]	0	NC [c]
0.3	4	5770 (1450)	3	10200 (1160)
0.5	7	8260 (3280)	5	14500 (6520)
1.0	2	(13300, 14000) [b]	2	(19200, 20700) [b]

NC = not calculated.

[a] Values are mean (SD).

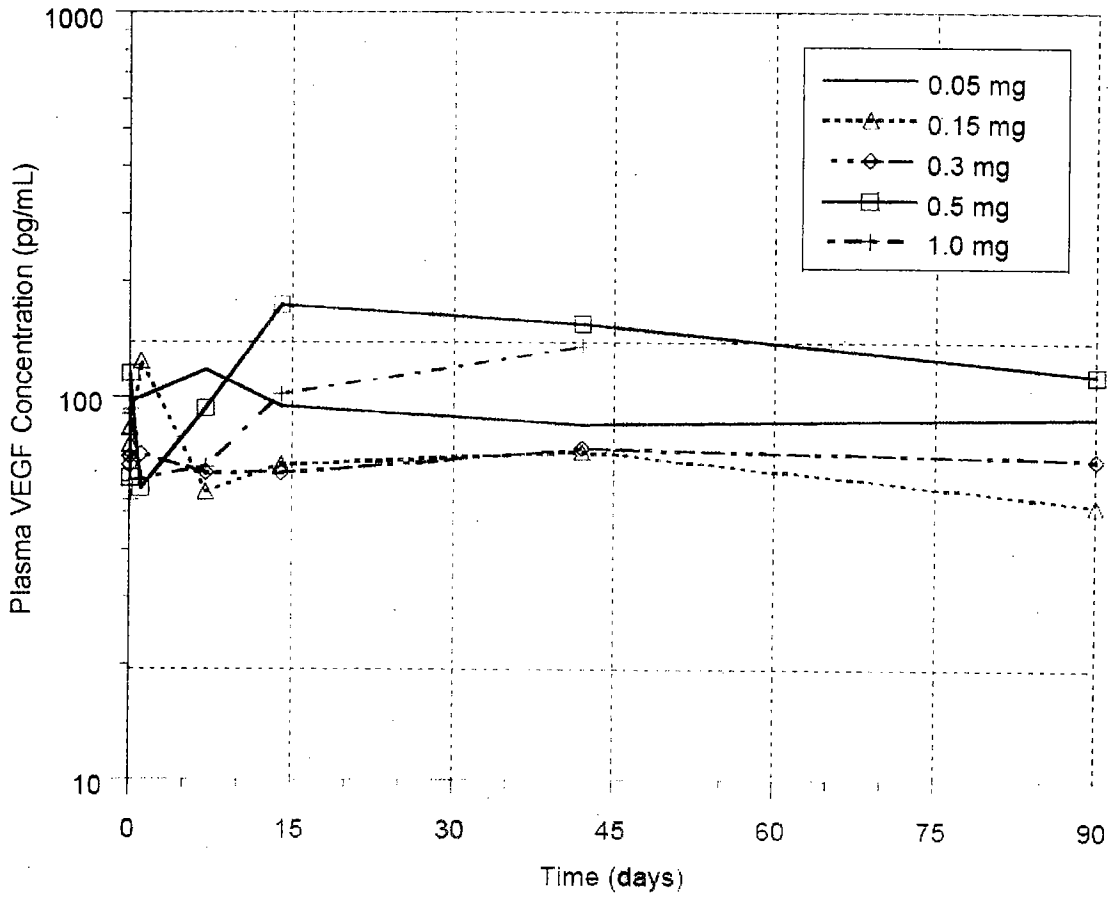
[b] For n=2, the range of values is reported instead of the mean (SD).

[c] The Day 14 sample was less than reportable for these subjects.

Endogenous plasma VEGF concentrations prior to ranibizumab administration ranged from <40 pg/ml (the lower limit of the reporting range) to171 pg/ml. the mean (n=6) VEGF plasma concentrations over time for these subjects are shown in Figure 2.

Figure 2

Average Plasma VEGF Concentrations over Time: Study FVF1770g



Following ranibizumab administration, VEGF concentrations fluctuated without any discernable pattern. The AUC_{0-t} and C_{max} for the mean VEGF plasma concentrations are shown in Table 8. Neither AUC_{0-t} nor C_{max} changed consistently with increasing doses of ranibizumab.

Table 8

Plasma VEGF Pharmacokinetic Parameters (Mean ± SD): Study FVF1770g

Dose Group (mg) (n [a])	AUC_{0-t} (×10 pg/mL•days)	C_{max} (pg/mL)
0.05 (5)	817±469	154±66
0.15 (4)	439±181	113±63
0.3 (4)	621±137	88.3±23
0.5 (6)	996±1041	210±113
1.0 (2)	437±47	161±25

[a] The n indicates the number of subjects for whom pharmacokinetic parameters were estimated.

Study FVF2425g

The primary objective was to investigate the safety and tolerability of ranibizumab administered as escalating, multiple-dose intravitreal injections in subjects with primary or recurrent subfoveal CNV secondary to AMD. The secondary objective of this study is to characterize the systemic PK of ranibizumab and VEGF concentrations over time following multiple-dose intravitreal injections of ranibizumab. Eligible subjects were randomized in a 1:1:1 ratio to receive one of three escalating-dose regimens of ranibizumab. Treatment regimens consisted of five, seven, or nine intravitreal injections of ranibizumab at 2 week or 4-week intervals, with doses ranging from 0.3 to 2.0mg. Serum concentrations of ranibizumab are summarized in Table 4. All screening samples for serum ranibizumab were below the limit of detection with the exception of one sample. After the start of treatment with ranibizumab, serum concentrations of ranibizumab were detected in more than 60% of the samples analyzed.

Table 9

Serum Ranibizumab Concentrations (ng/mL) of Treated Subjects: Study FVF2425g

Sampling Day	Timepoint	Group 1			Group 2			Group 3		
		n	Median	Range	n	Median	Range	n	Median	Range
Screening		9	<0.3	<0.3, <0.3	9	<0.3	<0.3, <0.3	10	<0.3	<0.3, 5.45
Day 0	Pre-dose	9	<0.3	<0.3, <0.3	10	<0.3	<0.3, <0.3	10	<0.3	<0.3, <0.3
	60 minutes	9	<0.3	<0.3, 0.901	10	<0.3	<0.3, 1.05	10	<0.3	<0.3, 1.22
Day 14	Pre-dose	9	0.402	<0.3, 1.12	10	<0.3	<0.3, 1.00	—	—	—
	60 minutes	9	0.688	<0.3, 0.904	10	<0.3	<0.3, 1.69	—	—	—
Day 28	Pre-dose	9	0.385	<0.3, 1.11	9	0.416	<0.3, 0.865	10	<0.3	<0.3, <0.3
	60 minutes	8	0.864	0.485, 26.5	9	1.32	0.646, 12.8	10	<0.3	<0.3, 2.25
Day 42	Pre-dose	9	0.711	<0.3, 2.10	9	0.848	<0.3, 1.30	—	—	—
	60 minutes	9	1.31	<0.3, 2.39	9	1.46	0.567, 5.87	—	—	—
Day 56	Pre-dose	5	1.57	1.31, 2.69	8	1.04	<0.3, 2.11	9	<0.3	<0.3, <0.3
	60 minutes	5	3.56	2.41, 4.75	8	1.86	0.626, 3.06	8	0.288	<0.3, 4.68
Day 70	Pre-dose	—	—	—	9	1.38	0.403, 2.02	—	—	—
	60 minutes	—	—	—	9	1.92	0.631, 5.36	—	—	—
Day 84	Pre-dose	9	0.738	<0.3, 4.87	8	1.735	1.43, 2.18	9	<0.3	<0.3, 0.560
	60 minutes	9	0.990	0.455, 3.51	8	2.51	1.97, 5.65	8	0.920	<0.3, 4.87
Day 98	Pre-dose	—	—	—	9	2.09	0.712, 6.93	—	—	—
	60 minutes	—	—	—	9	2.92	1.06, 10.7	—	—	—
Day 112	Pre-dose	8	0.408	<0.3, 0.689	8	2.36	1.54, 2.99	8	<0.3	<0.3, 4.61
	60 minutes	8	0.553	<0.3, 13.6	8	3.84	2.71, 10.9	8	1.08	<0.3, 3.63

Source: CSR FVF2425g, Table 14.2/1.
Note: The dash (—) indicates that no sample was collected in that group at that timepoint.

Study FVF2128g

The primary objective was to investigate the safety and tolerability of ranibizumab administered to subjects as multiple intravitreal injections. A secondary objective was to characterize the systemic PK of ranibizumab and VEGF concentrations over time following multiple intravitreal injections of ranibizumab. The study was divided into a screening period and a treatment period, consisting of two parts. Eligible subjects were randomized in a 4:1 ratio to receive ranibizumab or usual care (the standard of care, as determined by their treating physician and/or investigator) during part 1 of their study participation. Subjects randomized to receive ranibizumab receive one injection every 4 weeks (for a total of four injection) beginning at the Week 0 visit. At the week 14 visit, subjects who were randomized to receive usual care could have elected to receive ranibizumab in Part 2 of the study, provided that they continue to meet eligibility criteria. These subjects received one injection every four weeks (for a total of four injections) beginning at the Week 16 visit. Tables 10 and 11 show the serum concentrations of ranibizumab during parts one and two of the treatment periods.

Table 10.

Serum Ranibizumab Concentrations (ng/mL): Part 1 of Study FVF2128g

Visit	Timepoint	0.3 mg (n=25)			0.5 mg (n=28)		
		n	Median	Range	n	Median	Range
Screening		22	—	(—, 2.78)	27	—	(—, —)
Day 0	Pre-dose	22	—	(—, —)	28	—	(—, —)
	60 minutes	23	—	(—, 5.33)	28	—	(—, 0.765)
Day 14	2 weeks	24	—	(—, 0.403)	27	—	(—, 0.638)
Day 28	Pre-dose	25	—	(—, 0.417)	27	—	(—, 4.64)
	60 minutes	25	—	(—, 6.27)	27	—	(—, 2.63)
Day 42	2 weeks	25	—	(—, 4.68)	26	0.364	(—, 1.83)
Day 56	Pre-dose	24	—	(—, 1.38)	28	—	(—, 1.81)
	60 minutes	25	—	(—, 1.55)	26	0.325	(—, 38.2)
Day 84	Pre-dose	24	—	(—, 0.700)	24	—	(—, 0.674)
	60 minutes	23	—	(—, 4.42)	24	—	(—, 19.6)
Day 98 [a]	2 weeks	24	—	(—, 0.635)	27	—	(—, 1.06)

Note: The dash (—) indicates a less than reportable value.

[a] Final visit for Part 1 of study.

Source: CSR FVF2128g, Table 14.2/31.1.

Table 11.

Serum Ranibizumab Concentrations (ng/mL): Part 2 by Treatment Received in Parts 1 and 2 of Study FVF2128g

Visit	Timepoint	Usual Care/ 0.3 mg (n=4)			Usual Care/ 0.5 mg (n=5)			0.3 mg/ 0.3 mg (n=20)			0.5 mg/ 0.5 mg (n=22)		
		n	Med	Range	n	Med	Range	n	Med	Range	n	Med	Range
Day 112	Pre-dose	4	—	(—, —)	5	—	(—, —)	13	—	(—, 24.8)	18	—	(—, 2.05)
	60 minutes	4	—	(—, —)	4	—	(—, 1.88)	13	—	(—, 1.89)	16	—	(—, 2.80)
Day 140	Pre-dose	4	—	(—, —)	5	—	(—, —)	16	—	(—, —)	22	—	(—, 0.594)
	60 minutes	4	—	(—, 1.16)	4	—	(—, 1.98)	15	—	(—, 0.777)	20	—	(—, 1.59)
Day 168	Pre-dose	4	—	(—, —)	5	—	(—, —)	18	—	(—, —)	22	—	(—, 0.682)
	60 minutes	3	—	(—, 0.981)	5	—	(—, 0.944)	17	—	(—, 1.73)	21	—	(—, 1.90)
Day 196	Pre-dose	4	—	(—, —)	5	—	(—, —)	19	—	(—, —)	22	—	(—, 0.386)
	60 minutes	4	—	(—, 0.941)	5	—	(—, 0.855)	18	—	(—, 2.35)	19	—	(—, 5.26)
Final	2 weeks	4	—	(—, 0.466)	5	—	(—, 0.732)	19	—	(—, 0.818)	19	—	(—, 1.60)

Note: The dash (—) indicates a less than reportable value.

Source: CSR FVF2128g, Table 14.2/31.2

Most of the measurable results are below the ranibizumab concentration expectedt o impact VEGF-mediated activity (~10ng/ml).Out of 51 subjects who received an initial dose of 0.3mg ranibizumab in Part 1 and had a 1-hour post-dose sample, 14 (28%) had a measurable ranibizumab concentration ($\geq$0.300 ng/ml) at that timepoint (range, 0.303-5.33 ng/ml). Two of the 52 subjects (4%) who received an initial dose of 0.3mg and had a pre-dose sample at 4 weeks had a measurable ranibizumab concentration at that timepoint (0.417 and 4.64 ng/ml). One of the 24 subjects (4%) who received three doses of 0.3mg ranibizumab and had a pre-dose sample 4 weeks after the third dose had a measurable ranibizumab concentration at that timepoint (0.700 ng/ml). Of the 24 subjects who received an initial 0.3mg dose followed by two 0.5mg doses and had a pre-dose sample 4 weeks after the third dose, three (13%) had a measurable ranibizumab concentration at that timepoint (0.426, 0.509, and 0.674 ng/ml).

Plasma VEGF concentrations: In the 0.3mg group, the median plasma VEGF concentration at screening was 63.0 pg/ml, with a maximum concentration of 854 pg/ml. In the 0.5 mg group, the median plasma VEGF concentration at screening was less than reportable, with a maximum concentration of 159 pg/ml. In the usual-care treatment group, the median plasma VEGF concentration at screening was 40.4 pg/ml, with a maximum concentration of 146pg/ml. The plasma VEGF concentrations measured in subjects over the course of ranibizumab administration in this study did not change significantly relative to the pre-treatment screening sample concentrations.

Study FVF2428g

The primary objectives were to investigate the safety and tolerability of ranibizumab when administered to subjects as multiple intravitreal injections in combination with verteporfin PDT and to assess the effect of ranibizumab in the study eye, when administered with verteporfin PDT on the proportion of subjects losing fewer than 15 letters in visual acuity 12 months after study entry. A secondary objective was to characterize the systemic PK of ranibizumab and VEGF concentrations over time following multiple intravitreal injection of ranibizumab when administered with verteporfin PDT.

A majority of serum ranibizumab were below the limit of detection. The plasma VEGF concentrations measured in subjects during the study did not appear to change relative to the pre-treatment screening sample concentrations.

Phase III

Study FVF2598g

The primary objectives were to evaluate the efficacy of intravitreal injections of ranibizumab administered monthly in preventing vision loss, as measured by the proportion of subjects who lost fewer than 15 letters in visual acuity at 12 months compared with baseline, and to evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly. Serum samples to determine ranibizumab concentrations were drawn at baseline, month six, and month 12 for the enrolled subjects. Table 12 shows the ranibizumab concentrations.

Table 12.
Serum Ranibizumab Concentrations (ng/mL): Pharmacokinetic-Evaluable Subjects in Study FVF2598g

		Ranibizumab	
	Sham (n=218)	0.3 mg (n=226)	0.5 mg (n=225)
Month 6			
Number of serum samples	132	130	139
Number of samples LTR	132 (100%)	125 (96.2%)	133 (95.7%)
Maximum concentration	LTR	2.05	2.18
Month 12			
Number of serum samples	205	221	217
Number of samples LTR	204 (99.5%)	215 (97.3%)	204 (94.0%)
Maximum concentration	1.27	2.36	2.10

LTR=less than reportable (<0.3 ng/mL).
Source: CSR FVF2598g, Table 14.2/45.

Approximately 94% of the serum samples contained lower than reported concentrations of ranibizumab. A vitreous sample was obtained 15 days after the Month 2 injection from Subject 141005 (0.5mg group). The concentration of ranibizumab was 12.0 µg/ml. The measured concentration of this vitreous sample was compared with the subjects individual predicted vitreous concentration-time profile based on the final population PK model for ranibizumab. With the volume of vitreous humor fixed at 4ml, the model predicted vitreous concentration would be 40.9 µg/ml. Compared with the observed concentration, the values were of the same order of magnitude and the model prediction was approximately three times larger than the observed concentration. The vitreous sample was obtained from a subject who had an adverse event as a result of an iatrogenic traumatic cataract.

Study FVF2587g
The primary objectives of the study were to evaluate the efficacy of intravitreal injections of ranibizumab administered monthly to subjects compared with verteporfin PDT in preventing vision loss, as measured by the proportion of subjects losing fewer than 15 letters in visual acuity at 12 months compared with baseline, and to evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly. Serum PK samples were drawn for enrolled subjects prior to therapy, month six, month 12 and month 24. Approximately 94% or more of the serum samples had lower than reported concentrations of ranibizumab at all timepoints. Table 13 shows the serum ranibizumab concentrations.

Table 13
Serum Ranibizumab Concentrations (ng/mL): Pharmacokinetic-Evaluable Subjects: Study FVF2587g

		Ranibizumab	
	Verteporfin PDT (n=136)	0.3 mg (n=135)	0.5 mg (n=137)
Screening			
Number of serum samples	59	52	52
Number of LTR samples	59 (100%)	51 (98.1%)	52 (100%)
Maximum concentration	0	8.270 [a]	0
Month 6			
Number of serum samples	115	121	116
Number of LTR samples	115 (100%)	118 (97.5%)	109 (94.0%)
Maximum concentration	LTR	16.000 [b]	1.220
Month 12			
Number of serum samples	126	124	128
Number of LTR samples	126 (100.0%)	123 (99.2%)	123 (96.1%)
Maximum concentration	LTR	30.700 [b]	0.968

LTR=less than reportable (0.3 ng/mL).

[a] One subject (343010) had measurable ranibizumab concentration at screening.

[b] One subject (334003) received Avastin® (bevacizumab) from 29 March 2004 (treatment ongoing at the time of the Month 6 sample) to 13 June 2004 (136 days prior to the Month 12 sample).

Source: CSR FVF2587g, Tables 14.1/7 and 14.2/47.

Four vitreous tissue samples were obtained from three subjects who underwent medically necessary vitrectomy. The vitreous concentrations of ranibizumab for these subjects are presented in Table 14.

Table 14

Vitreous Ranibizumab Concentrations: Study FVF2587g

Subject	Treatment Group	Timing of Sample Collection			Result (µg/mL)
		Study Day [a]	Last Prior Injection Visit [b]	Days after Last Prior Injection	
303001	0.3 mg	61	Month 1	25	0.872
339004	0.5 mg	100	Month 2	43	1.340
381008	Verteporfin PDT	149	Month 5	1	LTR
381008	Verteporfin PDT	191	Month 6	2	LTR

LTR=less than reportable (15.6 ng/mL).

[a] Day 0 was Study Day 1.

[b] Last ranibizumab or sham injection visit prior to sample collection.

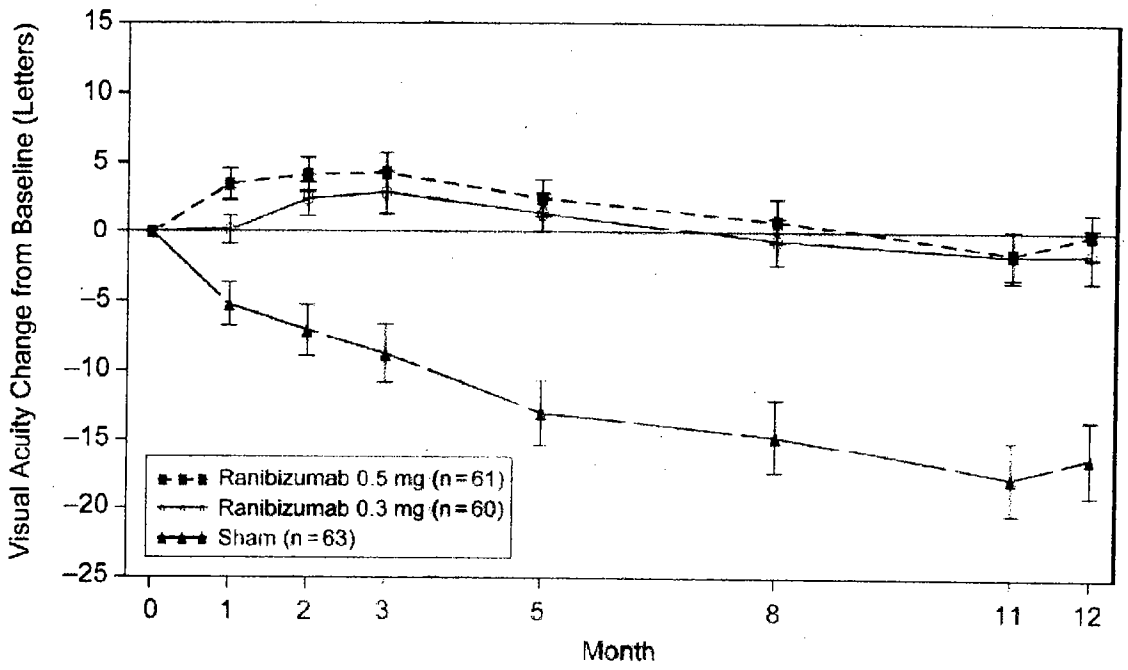
Based upon the population PK analysis that was performed for previous ranibizumab clinical studies, the predicted vitreous concentration for Subject 303001 25 days after the second injection of 0.3mg ranibizumab would be 10.8µg/ml (95% confidence interval [CI], 4.64-20.9 µg/ml), and for subject 339004 43 days after the third injection of 0.5mg ranibizumab would be 4.45 µg/ml (95% CI, 1.05-13.8 µg/ml). Subject 303001 experienced a retinal detachment, which was diagnosed three days prior to vitrectomy surgery. The retinal detachment may have provided for additional clearance pathway for ranibizumab, as the observed vitreous concentration was approximately 12-fold lower than the population means prediction. The observed vitreous ranibizumab concentration for subject 339004 was approximately 3.3-fold lower than the population mean prediction, but within the 95% CI estimate. Based upon limited data, the observed value is very similar to the predicted value. The subject had an event of macular hemorrhage.

Study FVF3192g

This was a phase IIIb, multicenter, randomized, double-masked, sham injection-controlled Study of the efficacy and safety of ranibizumab in subjects with subfoveal Choroidal neovascularization (CNV) with or without classic CNV secondary to age-related macular degeneration. The primary objectives of the study were to evaluate the efficacy of intravitreal injections of ranibizumab administered monthly for three doses followed by doses every three months in preventing vision loss, as measured by the mean change in best corrected visual acuity (BVCA) from baseline to 12 months. Also, to evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly for three doses followed by doses every three months. No pharmacokinetic sampling was performed. Figure 3 shows the mean change in visual acuity for 12 months.

Figure 3. Primary Endpoint: Mean change in Best Corrected Visual Acuity at 4 meters from baseline to 12 months

Note: $p \leq 0.02$ for all comparisons versus sham from Month 1 to Month 12.



Note: Vertical bars are ± 1 standard error of the mean.

This data shows that the visual acuity change from baseline initially improved until approximately month five to six, when the patient's vision returned to baseline and subsequently worsened. This data indicates that the every three month dosing schedule is not optimal and dose not produce the desired results that patients received when administered the drug at monthly injections.

4.3 Pharmacometric Review

4.3.1 Data

Genentech performed a pharmacometric analysis on available PK data from five clinical studies to develop a structural population PK model for ranibizumab disposition and to provide estimates for individual systemic exposure following intravitreal administration to support systemic exposure-safety analysis. A summary of the fraction of measurable samples by sampling timepoint is shown in Table 15.

Table 15. Measurable Serum Samples of All Subjects per Study and per Sampling Timepoint

No. of Measurable Serum Samples/ No. of All Serum Samples (%) [a, b]	Study					
	FVF1770g	FVF2425g	FVF2128g	FVF2428g	FVF2598g	All Studies
1 hour (0–0.5 days)	7/24 (29.2)	142/181 (78.5)	124/371 (33.4)	2/14 (14.3)	5/21 (23.8)	280/611 (45.8)
Day 1 (0.5–4 days)	24/27 (88.9)	0/0 (NA)	0/0 (NA)	2/3 (66.7)	3/8 (37.5)	29/38 (76.3)
Day 7 (4–10 days)	15/27 (55.6)	0/1 (0)	5/7 (71.4)	93/101 (92.1)	1/1 (100)	114/137 (83.2)
Day 14 (11–17 days)	9/23 (39.1)	80/94 (85.1)	51/156 (32.7)	60/102 (58.8)	2/4 (50)	202/379 (53.3)
Day 30 (27–33 days)	0/0 (NA)	14/40 (35)	11/206 (5.3)	10/308 (3.2)	7/320 (2.2)	42/874 (4.8)
Day 42 (39–45 days)	0/20 (0)	0/1 (0)	0/5 (0)	0/15 (0)	1/29 (3.4)	1/70 (1.4)
Day 90 (87–93 days)	0/18 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/2 (0)	0/21 (0)

NA=not applicable (no sample was collected within this time range).

[a] Includes all serum samples collected, including LTR and measurable samples from all 665 subjects in 051181_AllPatients_FINAL.csv.

[b] A time range was assigned to each scheduled sampling timepoint to account for variability in actual sampling time; not all samples were accounted for with the time range assignment.

The systemic exposure of ranibizumab following intravitreal administration was very low at all dose levels studied. Study FVF1770g had more samples drawn in the early part of the trial than other studies included in the analysis. Although the current validated ECLA assay of serum samples had an LLOQ of [redacted] only 4.8% of 874 samples collected at or around Day 30 had measurable concentrations and 45.8% of samples collected at or around one hour post-dose had measurable concentrations. Approximately 70% of the serum samples that are summarized in Table 15 were collected at or around Day 30 or one hour post-dose, which rendered the samples with measurable concentrations to be a small fraction of the total sample collected.

4.3.2 Population Pharmacokinetic Model

A one-compartment model with first-order absorption from the vitreous into the central compartment and first-order elimination from the central compartment best described the serum concentration-time data. The sponsor assessed both nonlinear and transit models but a linear model provided the best fit for the current data over the dose range of 0.05 to 2.0 mg/eye.

The sponsor evaluated the effects of 19 covariates on K_a, CL/F, and V_c/F. Creatinine clearance (CrCL) was found to explain only 7.57% of the between-subject variability of CL/F. This covariate was retained in the model. Concomitant verteporfin photodynamic therapy (PDT) was found to be a significant covariate for Ka. The fraction of between-subject variability explained by PDT was 33.6%. Subjects with one or more PDT treatments had 36% lower Ka than those who had never received PDT therapy. There is biological support for PDT as a covariate.

The final models for CL/F and K_a were parameterized as follows, with no covariate model for V_c/F:

$$\hat{CL} = \Theta_1 (CrCL/CrCL_{median})^{\Theta_2}$$

$$Ka = \Theta_3 (1+\Theta_4 PDT)$$

Where: Θ_1 = Typical CL/F (L/day)
Θ_2 = Typical V_c/F (L)
Θ_3 = Typical K_a (day^{-1})
Θ_4 = Covariate exponent for CL/F (for CrCL)

The population parameter estimates for the final model are summarized in Table 16. There is a relative large residual error (36.5%). The sponsor suggested that the residual error may be related to inter-occasional variability which was not included in the model.

Table 16. Population Parameter Estimates with CV (%) for the Combined Full Model and Combined Full Model with PDT and the Final Covariate Model

Parameter	Combined Full Model CL/F-CrCL & K_a-AGE	Combined Full Model with PDT on K_a CL/F-CrCL & K_a-AGE-PDT	Final Covariate Model CL/F-CrCL & K_a-PDT
MOF	–511.396	–524.914	–522.999
Typical CL/F (L/day)	24.8 (3.23)	23.6 (3.73)	23.8 (3.87)
CrCL on CL/F	0.244 (38.0)	0.230 (39.7)	0.266 (32.2)
% of variance explained	—	—	7.57
% change of CL/F at 5th percentile	—	—	–13.87
% change of CL/F at 95th percentile	—	—	15.82
Typical K_a (day^{-1})	0.0672 (5.58)	0.0786 (6.70)	0.0800 (6.70)
AGE on K_a	1.28 (39.9)	0.707 (71.0)	NA
PDT on K_a	NA	–0.329 (23.1)	–0.356 (20.2)
% of variance explained	—	—	33.64
K_a without PDT	—	—	0.0800
K_a with PDT	—	—	0.0515
Typical V_c/F (L)	2.65 (12.3)	2.96 (12.3)	2.97 (12.4)
$\omega_{CL/F}$ (%)	31.8 (15.6)	31.1 (17.0)	31.4 (17.2)
$\omega_{Vc/F}$ (%)	81.7 (26.8)	80.2 (25.5)	79.3 (25.6)
ω_{Ka} (%)	36.2 (25.0)	30.7 (36.1)	30.5 (40.8)
σ_{prop} (%)	36.5 (9.25)	36.5 (9.10)	36.5 (9.10)

ω=standard error of inter-individual variability for random effects distribution; σ_{prop}=SD describing the proportional component of residual variability; MOF=minimum value of the NONMEM objective function.

4.3.3 Deterministic Simulations

To support the dosing regimen, the sponsor conducted deterministic simulations of ranibizumab serum and vitreous concentration-time profiles using the two dosing regimens currently under investigation:

- [redacted] 0.5 mg/eye monthly ITV administration
- [redacted] 0.5 mg/eye monthly ITV administration for 3 months followed by quarterly ITV administration (quarterly regimen)

The distribution of ranibizumab in the vitreous humor was assumed to be homogeneous. Simulations were conducted for 500 subjects using the population parameters from the final model. A summary of pre- and post-dose predicted concentrations of ranibizumab in vitreous humor and serum (ie., C_{min} and C_{max}, respectively) is presented in Table 17.

Table 17. Median, 5th, and 95th Percentiles of Model-predicted Vitreous and Serum C_{max} and C_{min} at Steady-State

Steady-State Median (5th; 95th percentiles)	C_{max} (ng/mL)	C_{min} (ng/mL)
0.3 mg/eye monthly for 12 doses		
Serum	0.91 (0.47; 1.7)	0.13 (0.042; 0.29)
Vitreous	87,000 (77,000; 120,000)	12,000 (2,300; 41,000)
0.5 mg/eye monthly for 12 doses		
Serum	1.5 (0.79; 2.9)	0.22 (0.069; 0.49)
Vitreous	140,000 (130,000; 190,000)	20,000 (3,800; 68,000)
0.3 mg/eye monthly for 3 doses then quarterly for 3 doses		
Serum	0.77 (0.34; 1.7)	0.0021 (0.000022; 0.022)
Vitreous	75,000 (75,000; 79,000)	200 (1.0; 4,000)
0.5 mg/eye monthly for 3 doses then quarterly for 3 doses		
Serum	1.3 (0.57; 2.8)	0.0035 (0.000037; 0.037)
Vitreous	120,000 (120,000; 130,000)	330 (1.7; 6,600)

NA = not applicable.

Note: Simulation values at Month 11 pre- and post-dose are summarized as steady-state C_{min} and C_{max}, respectively, with a vitreous elimination half-life of 9 days.

It was estimated that the time required for ranibizumab to reach the maximum concentration in serum after ITV administration was 0.5 days. The simulations demonstrated that exposure of ranibizumab in the vitreous humor is approximately 90,000 times that in the systemic circulation after 0.3mg dose, and 140,000 times that in the systemic circulation after 0.5mg dose.