CENTER FOR DRUG EVALUATION AND RESEARCH

BLA APPLICATION NUMBER:

125156

MEDICAL REVIEW

Medical Officer's Review #3 – Labeling and Postmarketing Commitment

Application Type	BLA
Submission Number	125156
Primary Reviewer	Rhea Lloyd, M.D.
Date of Labeling Submission	June 28, 2006
Date of Postmarketing Commitment Submission	June 29, 2006
Date of Labeling Review	June 29, 2006
Name	Lucentis (ranibizumab injection)
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558

Submitted
The applicant has submitted labeling based on previous review, internal discussions and correspondence between the applicant and the Office of Antimicrobial Products with revisions to Section 12.2. In the second sentence of paragraph 2, the word "months" was capitalized. In the last sentence of paragraph 2, the phrase, [redacted] was replaced by "Foveal retinal thickness data."

Also submitted, as agreed during the 29 June 2006 teleconference between the Agency and the applicant, are the following additional Postmarketing Commitments:

1. Submit the final Clinical Study Report from Study FVF3689g by 30 June 2008.

2. Provide safety and efficacy data from a 2-year adequate and well-controlled clinical trial of a mutually acceptable design exploring multiple dosing frequencies of Lucentis. The timelines are outlined below:

Protocol Submission:	14 November 2008
Study Start:	21 September 2009
Final Clinical Study Report:	1 April 2013

Reviewer's Comment:
Acceptable.

7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1 of 4

Recommendations
It is recommended that BLA 125156 be approved with the labeling contained in this review.

The application supports the safety and effectiveness of Lucentis (ranibizumab injection) for the treatment of [redacted] neovascular [redacted] age related macular degeneration.

Rhea A. Lloyd, M.D.
Medical Officer, Ophthalmology

cc: William Boyd, MD
Wiley Chambers, MD
Janice Soreth, MD
Mark Goldberger, MD, MPH

Deputy Division Director Review

Application Type	BLA
Submission Number	125156
Established Name	Ranibizumab injection
Trademark	Lucentis
Therapeutic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558

Proposed Dosing Regimen
Lucentis is to be administered as an intravitreal injection 0.5 mg (0.05 mL) every one to three months.

Indication
Treatment of [redacted] neovascular [redacted] age related macular degeneration

Intended Population
Adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredients	Strength Amount	Amount per 0.05 mL Vial[a]	Function	Reference to Standard or Specification
Ranibizumab	[redacted]	[redacted]	Active ingredient	
α, α-trehalose dehydrate	[redacted]		[redacted]	
[redacted] histidine HCl [redacted]				Ph. Eur.
[redacted]				USP and Ph. Eur.
Polysorbate 20				NF and Ph. Eur.
Water for Injection				USP and Ph. Eur.

[a] Target fill volume of [redacted] per vial.

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EXECUTIVE SUMMARY

Recommendation on Regulatory Action

Lucentis (ranibizumab injection) with the labeling changes listed in this review is recommended for approval for the treatment of [redacted] neovascular [redacted] age related macular degeneration.

The applicant, Genentech Inc. has conducted three adequate and well-controlled studies, FVF2598g, FVF3192g, and FVF2587g which demonstrated statistically and clinically significant differences in the proportion of subjects who lose fewer than 15 letters in best corrected vision at 12 months compared with sham treatment.

Recommendation on Postmarketing Actions

Risk Management Activity

No post marketing risk management activity beyond the usual collection of adverse events is recommended.

Required Phase 4 Commitments

[redacted]

Other Phase 4 Requests

There are no other Phase 4 requests.

Summary

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection

Age Related Macular Degeneration (AMD) is clinically manifest in two distinct forms: the non-exudative (dry) or the exudative (wet) form of the disease. The etiology of the disease is such that new abnormal blood vessels proliferate from the choriocapillaris through defects in the Bruch's membrane under the retinal pigment epithelium (RPE), forming neovascular membranes. These new vessels leak serous fluid and may give rise to serous and hemorrhagic detachment of the RPE and neurosensory retina and may stimulate fibrous disciform scarring with subsequent loss of central vision.

Neovascular AMD is characterized by CNV in the macular region. Vascular endothelial growth factor-A (VEGF-A) has been observed in surgically excised human fibrovascular lesions. It is

reasonable to suggest that active forms of VEGF-A are targets for therapeutic intervention in neovascular AMD.

Efficacy
The three phase 3 studies submitted, Study FVF2598g, Study FVF2587g, and Study FVF3192g were designed to demonstrate the safety and efficacy of Lucentis (ranibizumab injection) in the treatment of neovascular AMD. All three studies were prospective, multicenter, randomized, double-masked, parallel group. Study FVF2598g and FVF3192g had sham controls, and Study FVF2587g had an approved photodynamic therapy as a control. All three studies demonstrated clinically and statistically significant differences between ranibizumab and the control arm. The effectiveness of dosing every three months appeared to be only one third as effective as monthly injections. Based on the population studied, there does not appear to be any difference in Lucentis' effect based on age, race, ethnicity or iris color.

Safety
The population studied was predominantly elderly and white which is representative of the population usually affected by age-related macular degeneration. The demographics of the patient population do not reflect problems with recruitment.

The most common adverse events identified are conjunctival hemorrhage, eye pain, increased intraocular pressure, retinal disorder and vitreous floaters. These adverse events are often associated with intravitreal injections.

Dosing Regimen and Administration
The sponsor has performed adequate dose ranging and dose frequency studies of Lucentis (ranibizumab injection). Lucentis has been proven safe and effective when administered as an intravitreal injection 0.5 mg/0.05 mL once monthly. This dosing regimen achieved and sustained a statistically significant difference in the proportion of patients who lost 15 letters of vision compared to baseline relative to the control group. When Lucentis is dosed every three months, it appears that 2/3 of the effectiveness is lost.

Drug-Drug Interactions
In Study FVF2587g, Lucentis (ranibizumab) was dosed with verteporfin PDT. Significant inflammation was observed when Lucentis was administered 7 days following PDT, but not when dosed at intervals longer than 7 days. No drug-drug interaction analyses were performed.

Special Populations
Subgroup analyses did not reveal any differences in the safety or efficacy with respect to age, sex, baseline visual acuity, CNV lesion type, lesion size, or prior laser photocoagulation. The population studied for this indication was predominantly elderly and white, reflective of the population most affected by this disease. The number of patients outside of this demographic group was too small to draw any definitive conclusion regarding the safety and efficacy. No pediatric trials were conducted for this drug as age-related macular degeneration is a disease seen only in adults.

INTRODUCTION AND BACKGROUND

Product Information

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection
Chemical Class	VEGF Inhibitor
Indication	Treatment of neovascular (wet) age-related macular degeneration

Currently Available Treatment for Indications

There are currently two approved drug products for the treatment of age related macular degeneration – Visudyne (verteporfin for injection) and Macugen (pegaptanib sodium injection). Visudyne was approved under NDA 21-119 on April 12, 2000, for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration. Macugen was approved under NDA 21-756 on December 17, 2004, for the treatment of neovascular (wet) age-related macular degeneration.

Availability of Proposed Active Ingredient in the United States

Ranibizumab is a new molecular entity and has not been marketed in the United States.

SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

CMC (and Product Microbiology, if Applicable)

Formulation

Ingredients	Strength: Amount per 10 mg/mL Vial[a]	Function	Reference to Standard or Specification
Ranibizumab	[redacted]	Active ingredient	
α, α-trehalose dehydrate	[redacted]		
histidine HCl			Ph. Eur.
[redacted]			USP and Ph. Eur.
Polysorbate 20			NF and Ph. Eur.
Water for Injection			USP and Ph. Eur.

[a] Target fill volume o[redacted] per vial.

Genentech intends to use a life-cycle approach for setting ranibizumab specifications. This life-cycle approach will use interim acceptance criteria based upon the limited data available at the time of submission. Since campaign-to-campaign variation can be larger than the variation within a campaign, Genentech proposes a post-approval commitment for re-evaluating the

interim acceptance criteria after three commercial post-approval campaigns (consisting of a minimum of – additional lots). The re-evaluation is expected to take place within two years after approval but will ultimately depend on the currently unknown manufacturing schedule for ranibizumab Drug Substance.

Lucentis Drug Product Release and Shelf-Life Specifications.

Test Code	Test Name	Acceptance Criteria	Release	Shelf-life

Animal Pharmacology/Toxicology

There were no significant findings in the pharmacology/toxicology reviews which would affect the clinical outcome.

DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

This review is based on the primary reviews from the Clinical, Pharmtox, Product Quality, Biopharm and Statistical staff and results of the applicant supported trials for AMD conducted under BBIND — Three phase 3 safety and efficacy trials were submitted to support the indication currently being sought by the applicant. In addition, the results of four phase 1/2 dose ranging and safety trials were also submitted. This NDA was submitted in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

Tables of Clinical Studies

Study	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)
FVF2587g	Randomized, double-masked, double-sham active treatment-controlled (US, Europe, Australia)	Subjects with predominantly classic subfoveal neovascular AMD	Verteporfin PDT (+sham injection)	423	Intravitreal injection q month, max. 24 injxns over 2 yrs, or verteporfin PDT q3mos as needed	0.3 mg (n=140); 0.5 mg (n=140), sham injection (n=143)
FVF2598g	Randomized, double-masked, sham-controlled (US)	Subjects with minimally classic or occult subfoveal neovascular AMD	Sham injection	716	Intravitreal injection q mo., max. 24 injxns over 2 years	0.3 mg (n=238), 0.5 mg (n=240), sham injection (n-238)
FVF3192g	Randomized, double-masked, sham-controlled (US)	Subjects with recurrent subfoveal CNV with or without classic CNV secondary to AMD	Sham injection	184	Intravitreal injection q month for 3 doses (Day 0, Month 1, Month 2) followed by doses q 3 months (Mos. 5, 8, 11, 14, 17, 20 and 23)	0.3 mg 0.5 mg sham injection (Target: 61-62 subjects per group)
FVF2508g	Extension (US)	Subjects with neovascular AMD who completed a Genentech Phase 1/2 ranibizumab study	None	70	Intravitreal injections every 28 days (± 5 days) through October 2006 or until 30 days after product launch	0.5 mg (n=66)
FVF2425g	Randomized, open-label, multiple-dose escalating regimens	Subjects with neovascular AMD	None	29	Intravitreal injections at 2- or 4-week intervals, max. of 5, 7 or 9 total injections	0.3 mg to 1.0 mg escalating regimen with 7 total injxns (n=9); 0.3mg to 2.0 mg

Study	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)
	(US)				over 16 weeks	escalating regimen with 9 total injxns (n=10); 0.3 mg to 2.0 mg escalating regimen with 5 total injxns (n=10)
FVF2128g	Randomized, open-label, dose-escalation (US)	subjects with classic neovascular AMD	Usual care[d]	64	Intravitreal injections q 4 weeks, maximum of 8 total injections over 28 weeks, or usual care with crossover to ranibizumab treatment after 14 weeks	0.3 mg (n=25), 0.3 mg initial dose escalated to 0.5 mg for subsequent doses 9n=28), usual care (n=11)
FVF1770g	Open-label, single-dose escalation (US)	Subjects with neovascular AMD	None	27	Single intravitreal injection	0.05 mg (n=6), 0.15 mg (n=6), 0.30 mg (n=6), 0.50 mg (n=7), 1.0 mg (n=2)
FVF2428g	Randomized, single-masked, sham-controlled, combination treatment (US)	Subjects with predominantly classic neovascular AMD	Verteporfin PDT (+sham injection)	162	Intravitreal injection q month, max. 24 injxns over 2 years, in combination with verteporfin PDT q3mos, as needed	0.5 mg (n=106), sham injection (n=56)
CRFB002A 1201	Open-label (Japan)	Subjects with subfoveal CNV secondary to AMD	None	Target 84	Intravitreal injections every month	0.3 mg 0.5 mg (Target: 42 subjects per group)
CRFB002B 2201	Open-label (Europe)	Subjects with occult or predominantly classic subfoveal CNV secondary to AMD	Verteporfin PDT	32	Intravitreal injections every month in combination with verteporfin PDT	0.5 mg (n=30)

Review Strategy

This review relies primarily on the results of the three Phase 3 trials submitted by the applicant.

The submitted clinical study reports, clinical protocols and literature reports related to trials FVF2598g and FVF2587g were reviewed. The application is in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

Data Quality and Integrity

There is no evidence that Phase 3 studies reviewed in this BLA were not conducted in accordance with acceptable clinical ethical standards.

There were no significant problems identified Division of Scientific Investigations (DSI) audits that are likely to affect the data quality. The case report forms for the three studies were provided by Genentech, and these were reviewed for completeness and quality.

Compliance with Good Clinical Practices

The studies were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practice (GCPs), the Declaration of Helsinki and in compliance with relevant local and national regulations for informed consent and protection of subject rights in the country of conduct.

Before initiation of the study, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The studies began only after receiving written approval from each EC/IRB.

Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence suggesting problems with the integrity of the submitted data.

CLINICAL PHARMACOLOGY

Pharmacokinetics – *See primary reviews.*

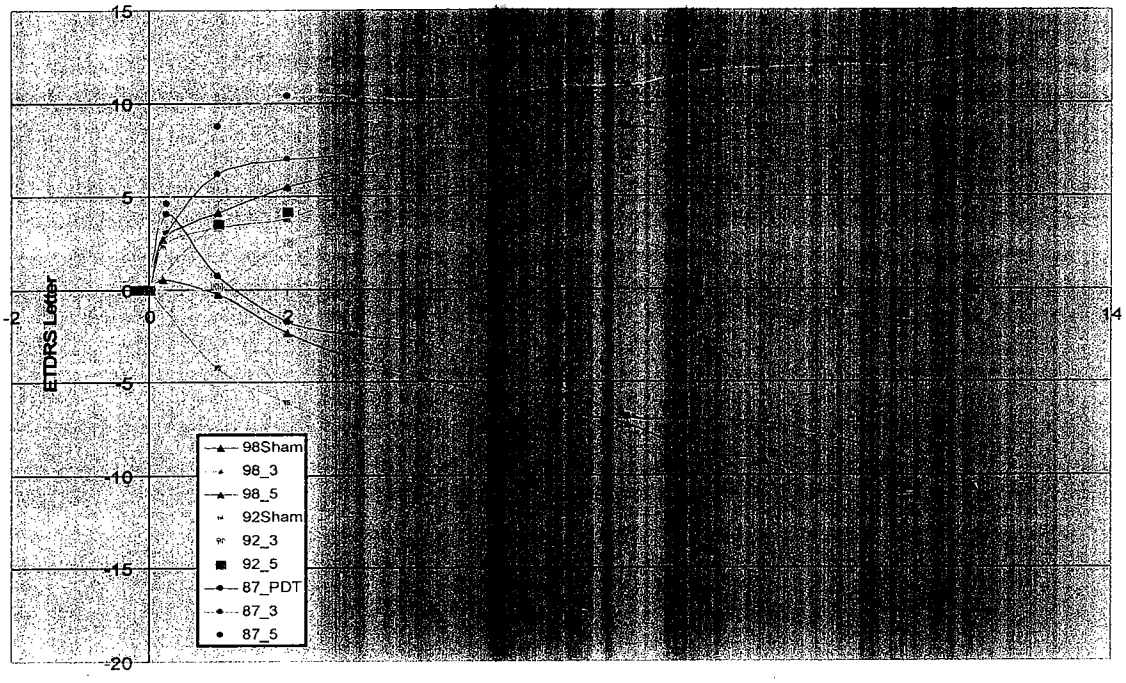
Pharmacodynamics – *See primary reviews.*

Exposure-Response Relationships

The retina is the site of disease in neovascular AMD. Therefore, systemic ranibizumab concentrations after intravitreal administration are not expected to correlate with efficacy.

INTEGRATED REVIEW OF EFFICACY

The study designs of the three Phase 3 studies are included in the Primary Medical Officer's Review. Additional analyses and cross comparisons between studies are presented below. It is recognized that there are potential risks in comparing across studies. With respect to treatment by an intravitreal route of administration, these studies utilized essentially the same population.



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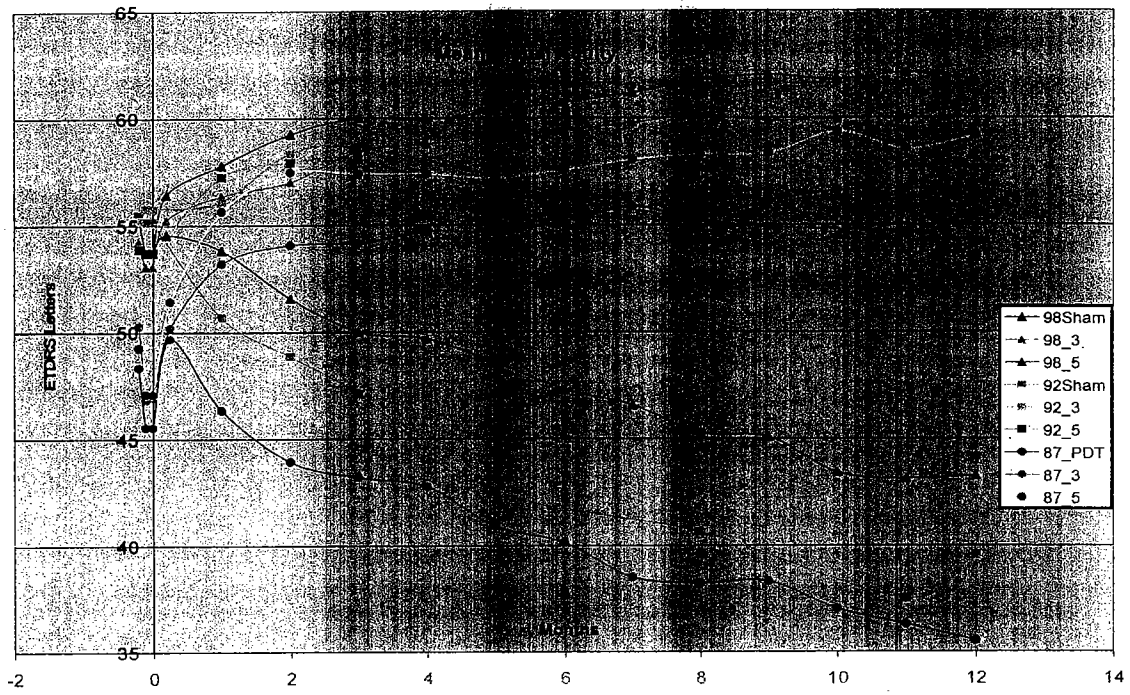

The 0.5 dose was consistently more effective than the 0.3 dose and each were more effective than the control group. The slope of the best fit line between month 3 and month 12 demonstrated a two thirds reduced effect of ranibizumab when the product was administered every three months compared to monthly treatments. The month 3-12 slopes for sham were -.87, -.85, -.84. The month 3-12 slopes for the 0.5 dose monthly were +.23 and +.26. The month 3-12 slope for the q3month injections was -.56. For the q3month injection, this becomes a 5 letter loss over the 9 month period

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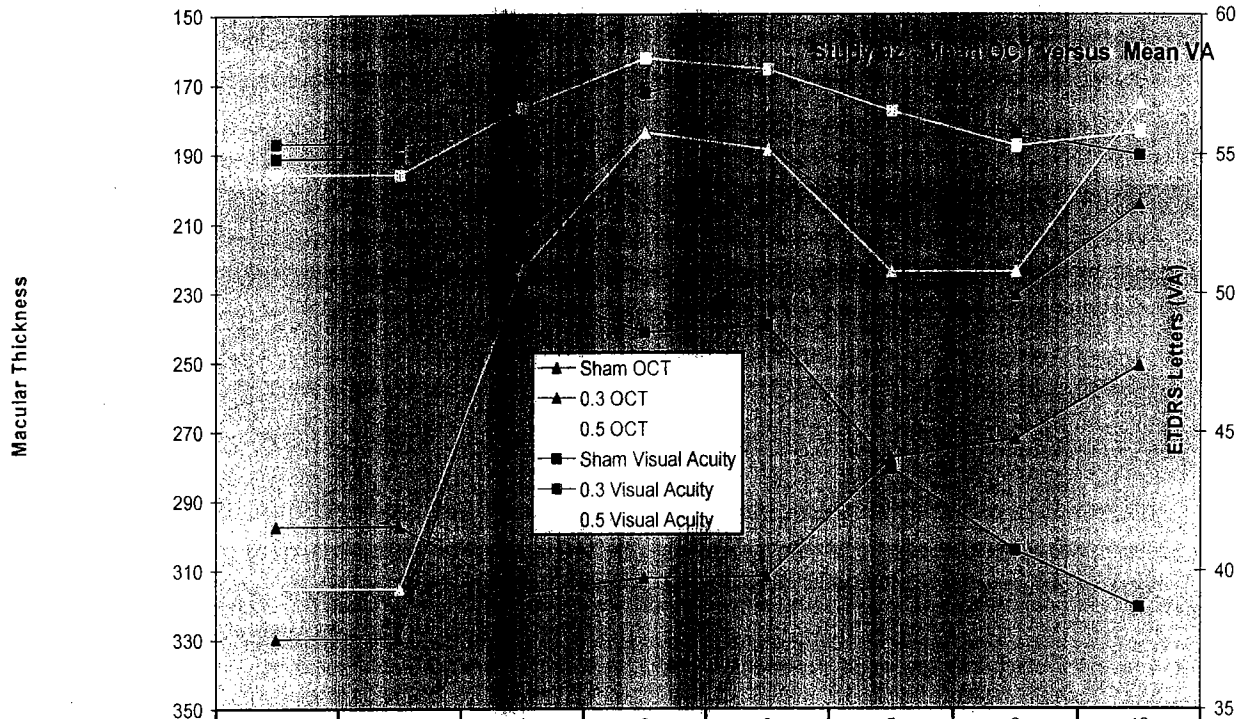

	-0.1	0	1	2	3	5	8	12
Sham OCT	297	297	317	312	312	278	272	251
0.3 OCT	330	330	213	183	189	214	231	205
0.5 OCT	315	315	223	184	189	224	224	175
Sham Visual Acuity	55	55	50	49	49	44	41	39
0.3 Visual Acuity	55	55	56	57	58	56	56	55
0.5 Visual Acuity	54	54	57	58	58	57	55	56

Noted above, there is no correlation between OCT and visual acuity. Treatment with ranibizumab results in a thinner macula even when the visual acuity decreases. The month 12 values illustrate this point. At month 12 for the ranibizumab 0.5 group, the mean macular thickness has its lowest value; however the visual acuity is at its worst.

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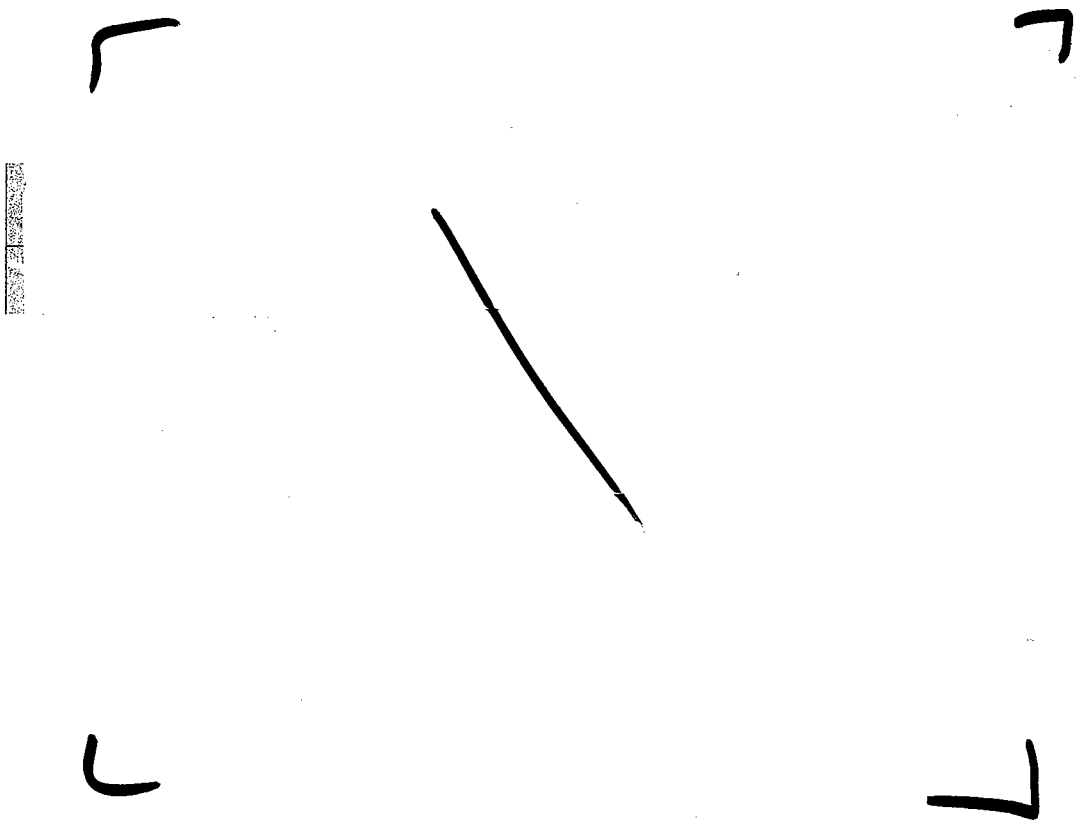

This graph illustrates that a substantially larger proportion of patients treated with ranibizumab injection develop thinner maculae and have improved visual acuity. While there is not a direct correlation between visual acuity and macular thickness over the course of this study, there is a general tendency for patients treated with ranibizumab to do both. For any individual patient, there is no significant correlation between macular thickness and visual acuity.

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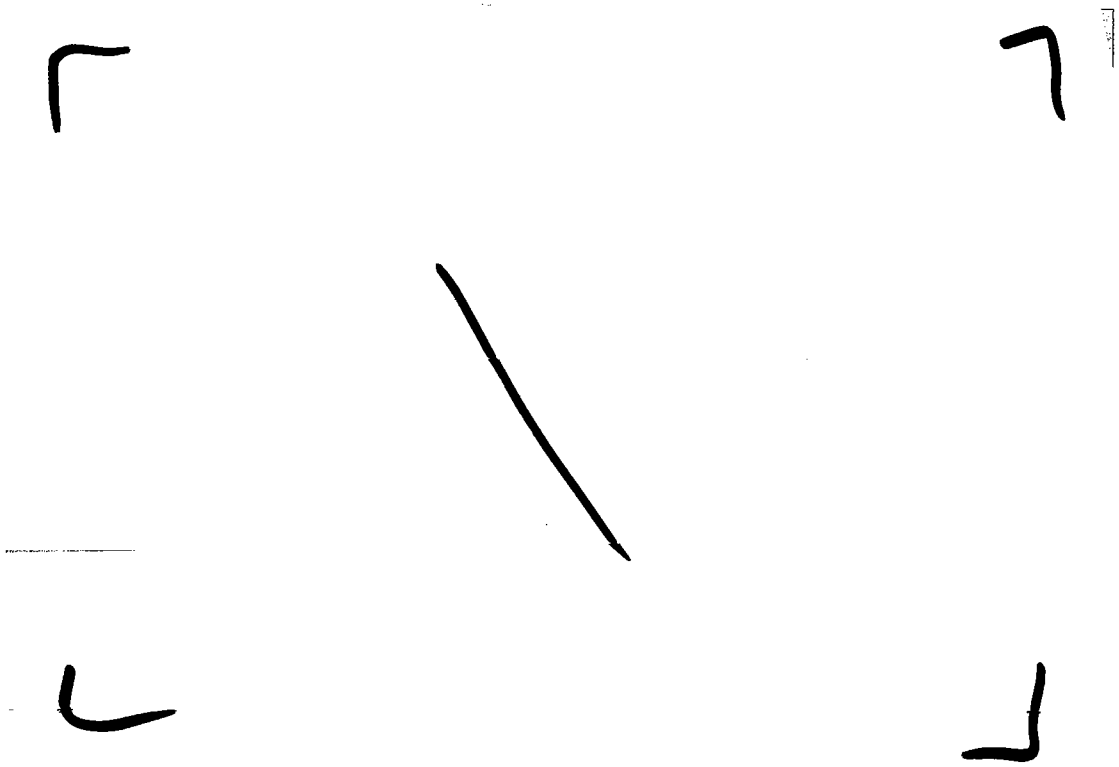

This graph presents a comparison between a change in OCT and the visual acuity at the next visit. Although not shown, data looks very similar for predictions of visual acuity at visits after the next visit. The graph illustrates that macular thickness is not predictive of visual acuity at later visits.

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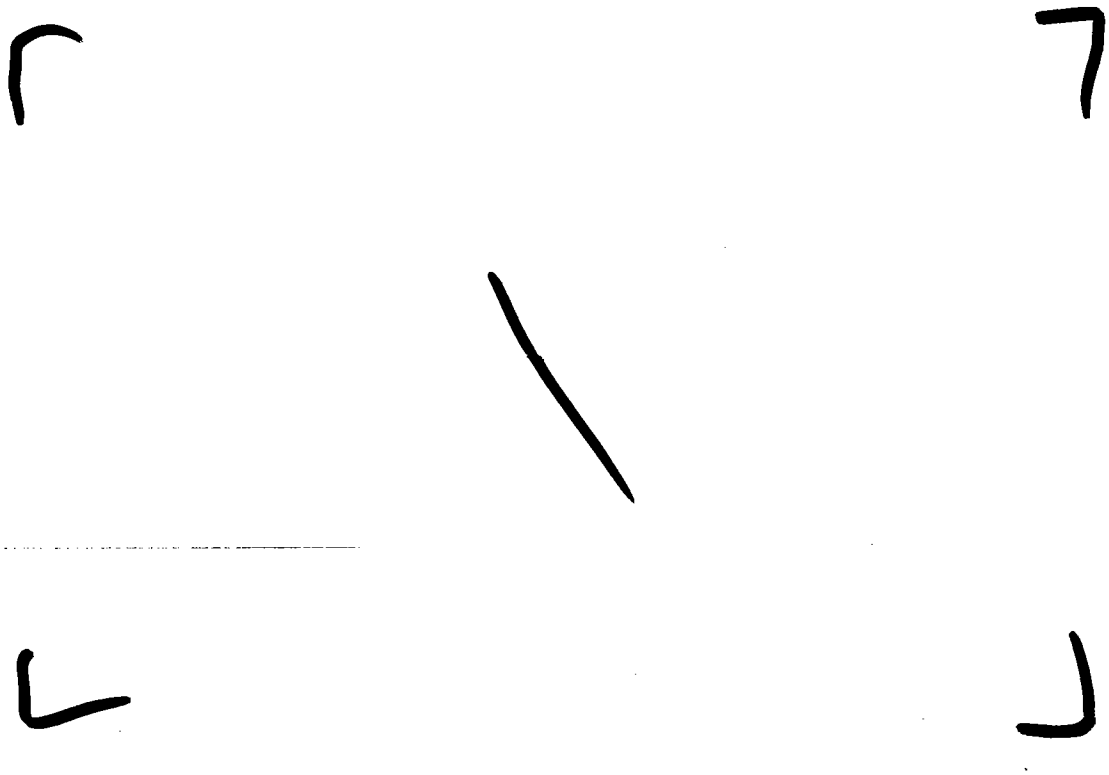

This graph illustrates the variation in visual acuity for any given macular thickness. While it is expected that thicker maculae will ultimately lead to poor vision, within the time frames of this study, there is no direct correlation between visual acuity and macular thickness. As a general rule, it appears that macular thickness below 200 often leads to better vision.

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An attempt was made to see if OCT criteria or vision loss criteria might have aided in the decision to treat patients with Lucentis. Although no formal criteria have been defined for normality of OCT, an increase in 100 microns might be considered the smallest change reliably available to use as a basis for treatment. In addition, although a 15 letter loss is the smallest clinically significant change, a single line change (5 letters) is commonly reported for safety parameters and was therefore investigated as a small visual acuity change. The results are listed below:

Percentage of Patients Meeting particular OCT or Vision Loss Criteria

OCT Increased by at least 100 or Vision Loss by 5 or more letters

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	64%	53%	75%	75%	78%
0.3	19%	38%	51%	54%	59%
0.5	5%	30%	43%	54%	54%

OCT Increased by at least 100

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	22%	11%	22%	17%	14%
0.3	0%	5%	16%	16%	11%
0.5	0%	0%	16%	16%	8%

Vision Loss by 5 or more letters

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	50%	47%	69%	69%	75%
0.3	19%	35%	41%	46%	59%
0.5	5%	30%	38%	54%	51%

OCT Increased by at least 100 with no loss of 5 or more letters

	Month 2	Month 3	Month 5	Month 8	Month 12
Sham	14%	6%	6%	6%	3%
0.3	0%	3%	11%	8%	0%
0.5	0%	0%	5%	0%	3%

As noted from the table, even a change as small as 100 microns or loss of 5 letters is not likely to have led to additional treatments and if used as the sole criteria would have resulted in fewer treatments than once every three months.

Efficacy Conclusions

The submitted pivotal studies in BLA 125156 Lucentis (ranibizumab injection) demonstrate the efficacy for the use of ranibizumab 0.5-mg in the treatment of neovascular age-related macular degeneration.

The submitted phase 3 studies both demonstrate a clinically significant treatment effect of ranibizumab [redacted] and 0.5-mg compared to sham and Verteporfin PDT, respectively, for the primary efficacy endpoint, the proportion of subjects with a loss of fewer than 15 letters in the best corrected visual acuity score at Month 12 compared with baseline.

Macular thickness is not predictive of current or future visual acuity, although macular thickness above 200 μm and particularly greater than 400 μm is associated with poorer vision. Ranibizumab is capable of doing more than just thinning the macula and vision may be lost in spite of a thin macula.

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INTEGRATED REVIEW OF SAFETY -Reported Adverse Events

Preferred Term		Max	Min	Sham Max	Sham Min	FVF2598g ab 0.5 mg N=238		FVF2598g ab 0.5 mg N=238		FVF2598g ab 0.3 mg N=238		FVF2598g ab 0.3 mg N=238		FVF2598g ab 0.3 mg N=238		FVF2598g ab 0.3 mg N=238	
Conjunctival hemorrhage	294	77%	43%	66%	29%	168	70%	181	76%	26	43%	87	62%	169	71%	184	77%
Macular degeneration	173	47%	23%	67%	39%	86	36%	109	46%	14	23%	50	36%	88	37%	111	47%
Eye pain	134	37%	18%	33%	11%	71	30%	89	37%	11	18%	34	24%	77	32%	86	36%
Vitreous floaters	102	32%	10%	10%	3%	53	22%	71	30%	6	10%	25	18%	59	25%	76	32%
Retinal hemorrhage	96	26%	17%	56%	37%	40	17%	58	24%	12	20%	26	19%	46	19%	61	26%
Intraocular pressure increased	92	24%	16%	7%	3%	39	16%	57	24%	13	21%	22	16%	38	16%	57	24%
Vitreous detachment	78	22%	10%	18%	13%	40	17%	53	22%	6	10%	19	14%	39	16%	52	22%
Eye irritation	66	19%	10%	20%	6%	36	15%	46	19%	6	10%	14	10%	34	14%	38	16%
Foreign body sensation in eyes	61	19%	7%	14%	6%	39	16%	45	19%	6	10%	10	7%	41	17%	43	18%
Nasopharyngitis	55	16%	5%	13%	5%	18	8%	38	16%	3	5%	14	10%	21	9%	32	13%
Hypertension	53	17%	6%	16%	8%	20	8%	39	16%	5	8%	9	6%	20	8%	41	17%
Lacrimation increased	49	17%	3%	16%	0%	27	11%	39	16%	2	3%	8	6%	32	13%	41	17%
Vitritis	45	13%	5%	3%	1%	22	9%	30	13%	3	5%	12	9%	13	5%	17	7%
Eye pruritus	44	13%	0%	12%	3%	17	7%	32	13%	0	0%	12	9%	18	8%	23	10%
Visual disturbance	43	14%	5%	9%	2%	23	10%	33	14%	3	5%	7	5%	20	8%	27	11%
Blepharitis	41	13%	3%	9%	4%	26	11%	32	13%	2	3%	7	5%	16	7%	26	11%
Subretinal fibrosis	38	13%	4%	19%	10%	10	4%	15	6%	5	8%	18	13%	18	8%	22	9%
Arthralgia	38	11%	4%	9%	0%	10	4%	27	11%	3	5%	8	6%	15	6%	26	11%
Headache	37	15%	3%	10%	3%	14	6%	24	10%	2	3%	11	8%	24	10%	36	15%
Retinal disorder	37	13%	0%	9%	0%	26	11%	30	13%		0%	7	5%	20	8%	27	11%
Ocular hyperemia	36	10%	5%	10%	1%	17	7%	24	10%	3	5%	9	6%	16	7%	24	10%
Bronchitis	35	10%	0%	8%	0%	13	5%	25	10%		0%	10	7%	15	6%	23	10%
Maculopathy	35	10%	3%	11%	3%	16	7%	23	10%	2	3%	10	7%	11	5%	20	8%
Visual acuity reduced	33	17%	4%	24%	10%	16	7%	24	10%	4	7%	5	4%	15	6%	26	11%
Detachment of retinal pigment epithelium	33	11%	4%	15%	3%	17	7%	22	9%	6	10%	5	4%	24	10%	27	11%
Dry Eye	33	10%	3%	8%	5%	23	10%	24	10%	2	3%	7	5%	10	4%	16	7%
Retinal degeneration	31	11%	2%	7%	1%	17	7%	24	10%	1	2%	6	4%	19	8%	25	11%
Cough	31	10%	3%	7%	2%	16	7%	25	10%	2	3%	4	3%	20	8%	23	10%
Ocular discomfort	31	8%	4%	5%	0%	10	4%	17	7%	5	8%	9	6%	15	6%	18	8%
Iritis	30	8%	2%	8%	1%	15	6%	19	8%	1	2%	10	7%	15	6%	19	8%
Vision blurred	29	14%	3%	8%	2%	19	8%	22	9%	2	3%	5	4%	22	9%	34	14%
Anemia	29	8%	4%	8%	3%	10	4%	18	8%	4	7%	7	5%	6	3%	17	7%
Nausea	28	9%	2%	6%	4%	13	5%	21	9%	1	2%	6	4%	14	6%	21	9%
Sinusitis	28	8%	2%	6%	4%	14	6%	20	8%	1	2%	7	5%	13	5%	18	8%
Upper respiratory tract infection	27	15%	2%	10%	4%	11	5%	18	8%	1	2%	8	6%	15	6%	36	15%
Back pain	27	10%	1%	9%	0%	13	5%	22	9%	3	5%	2	1%	14	6%	24	10%
Blood pressure increased	27	8%	2%	8%	0%	11	5%	20	8%	1	2%	6	4%	14	6%	16	7%
Conjunctival hyperemia	26	9%	0%	7%	0%	13	5%	17	7%	0	0%	9	6%	6	3%	7	3%
Urinary tract infection	25	9%	0%	8%	0%	10	4%	17	7%		0%	8	6%	12	5%	21	9%
Influenza	24	10%	2%	5%	1%	10	4%	19	8%	1	2%	4	3%	10	4%	23	10%
Posterior capsule opacification	23	8%	2%	5%	0%	6	3%	19	8%	1	2%	3	2%	8	3%	15	6%
Cataract	22	7%	2%	7%	2%	9	4%	13	5%	1	2%	8	6%	7	3%	17	7%
Arthritis	21	8%	0%	8%	2%	10	4%	19	8%	0	0%	2	1%	7	3%	17	7%
Retinal exudates	20	9%	2%	11%	3%	14	6%	16	7%	1	2%	3	2%	18	8%	21	9%
Dizziness	20	8%	2%	10%	2%	5	2%	11	5%	2	3%	7	5%	11	5%	18	8%
Cataract, nuclear	20	6%	3%	6%	2%	8	3%	9	4%	3	5%	8	6%	8	3%	10	4%
Constipation	19	7%	0%	8%	0%	0	0%	13	5%	2	3%	4	3%	0	0%	15	6%
Depression	19	6%	2%	7%	2%	9	4%	14	6%	2	3%	3	2%	5	2%	12	5%
Insomnia	18	6%	2%	6%	1%	11	5%	14	6%	1	2%	3	2%	6	3%	10	4%
Hypercholoesterolemia	17	8%	1%	5%	2%	7	3%	13	5%	2	3%	2	1%	4	2%	10	4%
Pneumonia	17	8%	0%	6%	3%	7	3%	11	5%	0	0%	6	4%	9	4%	18	8%
Injection site hemorrhage	17	5%	0%	2%	0%	8	3%	12	5%		0%	5	4%	2	1%	4	2%
Diarrhea	16	8%	2%	8%	0%	5	2%	10	4%	2	3%	4	3%	10	4%	18	8%
Photopsia	16	7%	0%	6%	0%	7	3%	12	5%		0%	4	3%	11	5%	16	7%
Pain in extremity	16	6%	1%	6%	0%	8	3%	13	5%	1	2%	2	1%	8	3%	15	6%
Anxiety	16	5%	2%	6%	0%	8	3%	12	5%	1	2%	3	2%	6	3%	10	4%
Atrial fibrillation	16	5%	2%	4%	2%	4	2%	11	5%	2	3%	3	2%	4	2%	10	4%
Gastroenteritis, viral	16	4%	3%	2%	0%	7	3%	10	4%	2	3%	4	3%	3	1%	3	1%
Chronic obstructive pulmonary disease	15	5%	0%	2%	0%	0	0%	11	5%	0	0%	4	3%	0	0%	5	2%
Gastroesophageal reflux disease	14	6%	0%	6%	2%	6	3%	9	4%	0	0%	5	4%	6	3%	15	6%
Diabetes mellitus	14	5%	2%	2%	0%	5	2%	9	4%	1	2%	4	3%	4	2%	7	3%
Dyspnea	14	5%	0%	3%	1%	2	1%	8	3%	0	0%	6	4%	7	3%	12	5%
Cataract, cortical	14	5%	1%	2%	1%	9	4%	11	5%	1	2%	2	1%	1	0%	3	1%
Eye discharge	13	9%	0%	8%	0%	7	3%	7	3%	0	0%	6	4%	16	7%	21	9%
Macular edema	13	7%	0%	11%	4%	10	4%	12	5%	1	2%	0	0%	3	1%	6	3%
Herpes zoster	13	5%	0%	2%	0%	5	2%	10	4%	3	5%	0	0%	8	3%	13	5%
Contusion	13	4%	2%	8%	2%	4	2%	9	4%	1	2%	3	2%	3	1%	10	4%
Fall	13	4%	2%	4%	1%	5	2%	9	4%	1	2%	3	2%	3	1%	7	3%
Blood glucose increased	13	4%	0%	5%	0%	4	2%	9	4%	0	0%	4	3%	4	2%	8	3%
Vitreous hemorrhage	13	4%	1%	3%	1%	3	1%	7	3%	1	2%	5	4%	5	2%	8	3%
Cataract NOS	12	13%	0%	11%	0%	31	13%		0%		0%	12	9%	24	10%		0%
Cardiac failure congestive	12	5%	1%	4%	2%	2	1%	6	3%	3	5%	3	2%	2	1%	10	4%
Rash	12	5%	0%	4%	2%	5	2%	9	4%	0	0%	3	2%	9	4%	11	5%
Punctate keratitis	12	5%	1%	4%	1%	4	2%	9	4%	1	2%	2	1%	6	3%	11	5%
Eyelid edema	12	4%	0%	3%	0%	7	3%	10	4%		0%	2	1%	7	3%	8	3%
Blood cholesterol increased	12	4%	0%	4%	1%	4	2%	9	4%	0	0%	3	2%	1	0%	2	1%
Corneal abrasion	12	4%	0%	3%	0%	6	3%	7	3%	0	0%	5	4%	4	2%	6	3%
Pruritus	12	3%	0%	2%	1%	4	2%	8	3%	0	0%	4	3%	4	2%	8	3%
Seasonal allergy	11	5%	0%	4%	0%	5	2%	9	4%		0%	2	1%	6	3%	11	5%
Diverticulitis	11	4%	2%	2%	0%	4	2%	7	3%	1	2%	3	2%	6	3%	9	4%
Syncope	11	4%	0%	4%	2%	6	3%	9	4%	0	0%	2	1%	2	1%	5	2%
Conjunctivitis, allergic	11	4%	0%	2%	1%	7	3%	9	4%	0	0%	2	1%	3	1%	5	2%
Edema peripheral	10	7%	0%	6%	0%	7	3%	10	4%		0%	0	0%	9	4%	17	7%
Chest pain	10	7%	0%	6%	0%	3	1%	9	4%	0	0%	1	1%	4	2%	10	4%
Corneal dystrophy	10	4%	0%	3%	0%	5	2%	7	3%	0	0%	3	2%	8	3%	10	4%
Asthma	10	4%	0%	3%	0%	7	3%	10	4%		0%	0	0%	5	2%	7	3%

Immunogenicity

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies.

The assay indicated positive results in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. All three treatment groups had increases in positive results during the treatment period.

Immunoreactivity to Ranibizumab in the First Treatment Year- Safety Evaluable Subjects

Visit	Study FVF2598g			Study FVF2587g		
	Sham	Ranibizumab		Verteporfin	Ranibizumab	
	Sham N=236	0.3 mg N=238	0.5 mg N=239	PDT N=143	0.3 mg N=137	0.5 mg N=140
Screening	5/215 (2.3%)	6/215 (2.8%)	7/218 (3.2%)	8/131 (6.1%)	12/125 (9.6%)	7/123 (5.7%)
Month 6	19/201 (9.5%)	15/211 (7.1%)	17/207 (8.2%)	6/114 (5.3%)	11/120 (9.2%)	10/116 (8.6%)
Month 12	20/206 (9.7%)	22/222 (9.9%)	26/219 (11.9%)	7/125 (5.6%)	9/123 (7.3%)	16/129 (12.4%)

Note: Table entries are numbers of subjects with positive immunoreactivity over numbers of subjects with evaluable samples. LTR=0.7 log titer.

Exploratory subgroup analyses based on immunoreactivity to ranibizumab were performed to determine whether the appearance of immunoreactivity was related to key safety and efficacy outcomes. The analysis population was divided into three subgroups: subjects who had a negative or missing test result at screening and negative post-baseline results, subjects who had a negative or missing test result at screening but at least one positive post-baseline result, and subjects who had a positive test result at screening. Visual acuity outcomes and the occurrence of intraocular inflammation and autoimmune adverse events were examined by treatment group for each immunoreactivity subgroup. No clinically relevant differences between immunoreactivity subgroups were identified in study FVF2598g.

In Study FVF5287g, with regard to intraocular inflammation adverse events, proportionately more ranibizumab-treated subjects who were immunoreactive at some timepoint experienced intraocular inflammation events than subjects who were never immunoreactive. Twenty- eight percent (5 of 18) of ranibizumab-treated subjects who were immunoreactive during treatment only and thirty-two percent of subjects (6 of 19) who were immunoreactive at baseline experienced inflammation adverse events in the study eye, compared with 10% of ranibizumab-treated subjects (23 of 230) who were never immunoreactive. Of the 12 verteporfin PDT-treated subjects who were immunoreactive at some timepoint, none experienced an intraocular inflammation adverse event.

Intraocular Inflammation in Subjects with Immunoreactivity Based on the Initial and Confirmatory Assays (.)
Studies FVF2428g, FVF2587g, FVF3192g (First Treatment Year) and FVF2598g (2-Year Treatment Period)
Safety Evaluable Subjects

Study	Treatment Group	Subject ID	Study Day / Visit of Positive Immunoreactivity Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
FVF2428g	Verteporfin PDT + sham	91103	34 / Month 1	1.200	No CRF found	---
	Verteporfin PDT + Ranibizumab 0.5 mg	91308	- 7 / Screening	0.884	No CRF found	
			366 / Month 12	0.767		
FVF2587g	Verteporfin PDT	319001	386 / Month 12	0.797	No	---
		334008	-12 / Screening	1.130	No	
			190 / Month 6	0.902	No	
		401002	-8 / Screening	1.820	No CRF found	
			186 / Month 6	1.780		
			361 / Month 12	1.800		
	Ranibizumab 0.3mg	321003	-7 / Screening	0.945	Yes – Vitritis	Screening and Month 1
		334003	176 / Month 6	2.300	Yes – Iritis	Month 4 [2]
		337012	-26 / Screening	0.938	Yes – Iritis	Month 5 [3]
		351004	344 / Month 12	2.190	No	---
		352006	-10 / Screening	2.070	No	---
			180 / Month 6	1.890	No	---
			362 / Month 12	1.860	No	---
		403003	-1 / Screening	0.910	No	---
	Ranibizumab 0.5mg	306020	174 / Month 6	1.530	Yes – Vitritis	Months 1 and 2
			362 / Month 12	1.850		
		337009	364 / Month 12	1.270	No	---
		342007	174 / Month 6	2.450	Yes – Iritis, Vitritis	Month 11 [4]
			360 / Month 12	3.060		
		346001	182 / Month 6	1.260	No	---
			361 / Month 12	1.770		
		389001	-28 / Screening	1.240		
			182 / Month 6	0.993	Yes – Uveitis [5]	Month 7
			365 / Month 12	0.952		
FVF2598g	Sham	102008	183 / Month 6	1.230	No	---
			358 / Month 12	2.090		

Study	Treatment Group	Subject ID	Study Day / Visit for Positive Immunoreactivity Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
			463 / Early term.	2.060		
		116002	723 / Month 24	2.560	No	
		139004	-28 / Screening	2.100	Yes – Iritis	Day 7
			176 / Month 6	2.060		
			358 / Month 12	2.170		
			729 / Month 24	2.340		
		150005	181 / Month 6	0.864	No	---
			393 / Month 12	0.863		
		182003	355 / Month 12	0.903	No	---
	Ranibizumab 0.3mg	101021	361 / Month 12	1.850	No CRF found	
			719 / Month 24	1.810		
		110004	728 / Month 24	1.490	No	---
		112002	716 / Month 24	0.866	No	---
		125007	183 / Month 6	0.918	No	---
		141009	721 / Month 24	1.270	No	
		143001	-13 / Screening	3.550	Iritis	Month 2
			177 / Month 6	3.740		
		146001	714 / Month 24	1.080	No	
		149006	364 / Month 12	3.150	Iritis	Month 15 [6]
			717 / Month 24	2.120		
		159013	360 / Month 12	2.000	No	
			724 / Month 24	1.890		
		165002	-21 / Screening	0.910	No	
			175 / Month 6	0.993		
			368 / Month 24	0.793		
		170010	365 / Month 12	2.770	No CRF found	
			715 / Month 24	2.800		
		177006	358 / Month 12	1.870	Iritis	Day 7
			717 / Month 24	1.850		
	Ranibizumab 0.5 mg	102001	722 / Month 24	0.922	No	
		104002	719 / Month 24	1.140	No	
		106002	722 / Month 24	1.130	No	
		122002	359 / Month 12	1.630	No	
			723 / Month 24	1.770		
		124003	722 / Month 24	0.782	No	
		126001	174 / Month 6	1.700	No	
			357 / Month 12	2.040		
			727 / Month 24	1.480		
		141008	181 / Month 6	1.570	No	
			362 / Month 12	1.940		
			726 / Month 24	2.340		

Study	Treatment Group	Subject ID	Study Day / Visit of Immunoreactivity Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
		141013	715 / Month 24	2.610	Vitritis	Day 0
		143010	722 / Month 24	2.440	No	
		152004	522 / Early Term.	0.752	No	
		153006	183 / Month 6	1.900	No	
			365 / Month 12	1.530		
			718 / Month 24	2.070		
		159017	716 / Month 24	0.780	No	
		167002	717 / Mont 24	1.230	No CRF found	
		188005	717 / Month 24	1.250	No	
FVF3192g	Sham	534001	-7 / Screening	2.520	Vitritis	Month 1
	Ranibizumab 0.5 mg	507018	357 / Month 12	0.875	No	
		522002	367 / Month 12	1.530	No	

1 In Study FVF2428g, intravitreal injections (sham or ranibizumab 0.5 mg) were given every month and verteporfin PDT every 3 months.
2 Iritis diagnosed 1 day after Month 4 injection.
3 Iritis diagnosed day of injection. Injection was not held.
4 No resolution of uveitis noted in CRFs submitted.
5 Uveitis diagnosed 3 days post Month 7 injection. Serious AE led to treatment discontinuation in Month 9.
6 Treatment discontinued.

The Immunoreactivity Assay still requires refinement (see Product Quality Review). Based on this assay, Titers above 3 were associated with Intraocular Inflammation in 100% of cases.

Thromboembolic Events

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

Type of Adverse Event	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239	Verteporfin PDT N=145	Ranibizumab 0.5 mg N=137	Ranibizumab 0.5 mg N=140
TOTAL [a]	**2 (0.8%)**	**8 (3.4%)**	**9 (3.8%)**	**3 (2.1%)**	**4 (2.9%)**	**8 (5.7%)**
Hypertension events	0	1 (0.4%)	0	0	0	0
Arterial thromboembolic events	2 (0.8%)	5 (2.1%)	8 (3.3%)	2 (1.4%)	2 (1.4%)	4 (2.9%)
Non-ocular hemorrhages	0	1 (0.4%)	0	0	2 (1.5%)	3 (2.1%)
Other potentially associated events	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

I concur with the Medical Officer's assessment that there is a trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition noted at Month 12, but not at 24 months, particularly in the ranibizumab 0.5-mg dose group. This includes trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria).

The sponsor applied the Antiplatelet Trialists' Collaboration (APTC) classification (Antiplatelet Trialists' Collaborations 1994) to the adverse events which mitigates some of these issues by focusing on a more restricted but well-defined spectrum of serious adverse events: vascular deaths (including deaths of unknown cause), nonfatal myocardial infarction, nonfatal ischemic stroke, and nonfatal hemorrhagic stroke.

APTC Arterial Thromboembolic Events during the First Treatment Year: Studies FVF2598g and FVF2587g

Type of Adverse Event	Study FVF2598g			Study FVF2587g			Pooled Ranibizumab 0.5 mg N=379
		Ranibizumab		Verteporfin PDT	Ranibizumab		
	Sham N=236	0.3 mg N=238	0.5 mg N=239	N=143	0.3 mg N=137	0.5 mg N=140	
TOTAL [a]	2 (0.8%)	3 (1.3%)	5 (2.1%)	3 (2.1%)	3 (2.2%)	6 (4.3%)	11 (2.9%)
Vascular deaths	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	3 (0.8%)
Nonfatal myocardial infarction	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	3 (2.1%)	4 (1.1%)
Nonfatal ischemic stroke	1 (0.4%)	1 (0.4%)	3 (1.3%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	4 (1.1%)
Nonfatal hemorrhagic stroke	0	0	0	0	0	0	0

Note: Arterial thromboembolic events, defined according to the Antiplatelet Trialists' Collaboration classification (1994), are presented.

When applying the APTC classification to the serious adverse events, there is an overall trend in the ranibizumab 0.5-mg dose group compared to subjects in other treatment groups, but this is only a trend, the numbers are small and it does not hold up for the 24 month data.

Human Carcinogenicity
No studies have been conducted.

Special Safety Studies
Safety analysis was based on an evaluation of other safety parameters, as well, which included visual acuity (best corrected), intraocular pressure, ocular signs by slit lamp examination and indirect ophthalmoscopy the results of which are included throughout the safety review.

Withdrawal Phenomena and/or Abuse Potential
Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

Human Reproduction and Pregnancy Data
There are no adequate and well-controlled studies in pregnant women. There was no inadvertent exposure to the product in pregnant women during the development program.

Assessment of Effect on Growth
The intended population for this product is adults with age-related macular degeneration, a disease that does not exist in the pediatric age group. This application contains no pediatric data.

Overdose Experience
This product has minimal overdose potential and no studies were performed. Planned initial single doses of ranibizumab injection 1.0 mg were associated with clinically significant intraocular inflammation in 2 of 2 patients injected. With an escalating regimen of doses beginning with initial doses of ranibizumab injection 0.3 mg, doses as high as 2.0 mg were tolerated in 15 of 20 patients.

Postmarketing Experience
This product has not yet been marketed.

ADDITIONAL CLINICAL ISSUES

Dosing Regimen and Administration
The sponsor has performed adequate dose ranging studies during the drug development program. Lucentis (ranibizumab) 0.5 mg dose has been demonstrated to be safe and effective in two Phase 3 clinical trials. The dosing interval in the two pivotal Phase 3 trials was once monthly resulting in the improvement and maintenance of visual acuity and function, and for the reduction of vascular leakage and retinal edema, in patients with neovascular (wet) age-related macular degeneration.

Drug-Drug Interactions
No important drug-drug interactions have been identified.

Special Populations
The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Subgroup analyses did not reveal any differences in the primary efficacy endpoint between males

and females. The safety profiles seen in males and females, including the types and rates of adverse events, are similar.

Trials for this indication were conducted in a population that was overwhelmingly elderly and Caucasian. This is reflective of the population in which age-related macular degeneration occurs and does not reflect a problem with study enrollment.

Pediatrics
The applicant requested a waiver of the pediatric study requirements for the original Biologics License Application. The waiver was requested because the disease under study age-related macular degeneration does not occur in the pediatric age group.

Advisory Committee Meeting
Not applicable. No Advisory Committee Meeting will be held regarding this application.

Literature Review
The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

Postmarketing Risk Management Plan
No postmarketing risk management plan has been submitted.

Other Relevant Materials
Comments received from DDMAC and the Office of Drug Safety have been incorporated in the labeling review as appropriate.

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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 2 of 4

OVERALL ASSESSMENT

Conclusions

The submitted studies in BLA 125156 are sufficient to establish efficacy for the use of ranibizumab 0.5 mg injection in the treatment of the neovascular age-related macular degeneration. The phase 3 studies demonstrate replicative results in the ability of ranibizumab to stabilize and prevent vision loss in patients with neovascular macular degeneration when give intravitreally every month when compared to sham and verteporfin PDT treatment. A clinically significant effective is still present if Lucentis is administered once every three months after the first four doses.

Recommendation on Regulatory Action

BLA 125156 is recommended for approval from a clinical perspective for [redacted] patients with neovascular (wet) age-related macular degeneration.

Recommendation on Postmarketing Actions

Risk Management Activity

Not applicable. No postmarketing risk management activity is recommended at this time.

Required Phase 4 Commitments

[redacted]

Wiley A. Chambers, MD
Deputy Division Director
Division of Anti-Infective and Ophthalmology Products

cc: **Rhea Lloyd**
William Boyd
Janice Soreth
Mark Goldberger

Clinical Team Leader Labeling Review
(Medical Officer's Review #2)

Application Type	BLA
Submission Number	125156
Primary Reviewer	Rhea Lloyd, M.D.
Clinical Team Leader	William M. Boyd, M.D.
Letter Date	December 29, 2005
Stamp Date	December 30, 2005
Date of Labeling Submission	June 13, 2006
Date of Labeling Review	June 13, 2006
Established Name	Ranibizumab injection
Trademark	Lucentis
Therapeutic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558

Submitted

Submitted is revised labeling based on previous review, discussion between the applicant and the Deputy Division Director on June 12, 2006, and input from the Study Endpoints and Label Development (SEALD) Team.

In this submission, the applicant has accepted all requested changes to the package insert.

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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 3 of 6

Recommendations

It is recommended that BLA 125156 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Lucentis (ranibizumab injection) for the treatment of [redacted] neovascular [redacted] age related macular degeneration

William M. Boyd, M.D.
Clinical Team Leader

WMB 6/28/06

CLINICAL REVIEW

Application Type	BLA
Submission Number	125156
Submission Code	Original
Letter Date	December 29, 2005
Stamp Date	December 30, 2005
PDUFA Goal Date	June 30, 2006
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	June 21, 2006
Established Name	Ranibizumab injection
(Proposed) Trade Name	Lucentis
Therapeutic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 650-225-1558
Priority Designation	1P

Proposed Dosing Regimen

Lucentis is to be administered as an intravitreal injection 0.5 mg (0.05 mL) once a month or once every three months after the initial — monthly injections.

Proposed Indication

[redacted]

Intended Population

Adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredients	Strength Amount per [redacted] mg/0.05 mL Vial	Function	Reference to Standard or Specification
Ranibizumab	[redacted]	Active ingredient	
α, α-trehalose dehydrate	[redacted]		
histidine HCl			Ph. Eur.
[redacted]			USP and Ph. Eur.
Polysorbate 20			NF and Ph. Eur.
Water for Injection			USP and Ph. Eur.

[a] Target fill volume of [redacted] per vial.

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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, Lucentis (ranibizumab injection) with the labeling changes listed in this review is recommended for approval for the treatment of patients with neovascular (wet) age-related macular degeneration

The applicant, Genentech, conducted two adequate and well-controlled Phase 3 studies, FVF2598g and FVF2587g which demonstrate statistical and clinical significance on the primary efficacy endpoint (i.e., the proportion of subjects who lose fewer than 15 letters in best corrected vision at 12 months compared with baseline).

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No post marketing risk management activity is necessary.

1.2.2 Required Phase 4 Commitments

1. Develop and validate assays to detect and characterize immune responses to ranibizumab:

   A. Develop and validate a confirmatory assay capable of detecting both IgG and IgM isotype responses.

   B. Develop and validate an assay to detect neutralizing anti-ranibizumab antibodies.

   The assay methodology and validation reports will be provided by September 28, 2007.

2. To characterize further the immune response to ranibizumab, serum samples collected in studies FVF2587g, FVF2598g, FVF3192g will be assayed using the validated methods described above in Postmarketing Commitment 1.— The data obtained will be analyzed to discover and evaluate any association between immunoreactivity and dosing frequency as well as any potential impact of immunoreactivity on efficacy or safety outcomes.

   Date of submission of protocol and statistical analysis plan: February 28, 2007

   Date of submission of final study report: September —, 2008

   The need for an additional clinical study will be determined based on the results from the analysis described above.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection

Age-related macular degeneration (AMD) is a common cause of severe and irreversible vision loss in older adults. AMD is clinically manifest in two distinct forms: the non-exudative (dry) or the exudative (wet) form of the disease. Though the exudative (wet) form represents approximately 10% of AMD cases, it is responsible for 80-90 % of the vision loss due the vascular leakage associated with the characteristic choroidal neovascularization. An estimated 150,000 new cases of neovascular AMD are diagnosed each year in the United States. As the median age of the population increases, it is likely that ophthalmologists will encounter increasing numbers of patients with AMD.

The etiology of the disease is such that new abnormal blood vessels proliferate from the choriocapillaris through defects in the Bruch's membrane under the retinal pigment epithelium (RPE), forming neovascular membranes. These new vessels leak serous fluid and may give rise to serous and hemorrhagic detachment of the RPE and neurosensory retina and may stimulate fibrous disciform scarring, with subsequent loss of central vision.

Neovascular AMD is characterized by CNV in the macular region. Vascular endothelial growth factor-A (VEGF-A) has been observed in surgically excised human fibrovascular lesions. VEGF-A is alternatively spliced and post-translationally cleaved to generate multiple active forms, of which at least two have been observed in excised human CNV lesions. An increase in VEGF-A expression has been noted in experimental models of CNV in rodents. In addition, transgenic mice with increased VEGF-A expression in photoreceptors or retina pigment epithelium developed neovascularization reminiscent of CNV seen in humans with neovascular AMD. These results suggest that active forms of VEGF-A are reasonable targets for therapeutic intervention in neovascular AMD.
Ranibizumab is a recombinant humanized antibody Fab fragment that neutralizes VEGF as a therapeutic intervention in neovascular AMD.

1.3.2 Efficacy

Study FVF2598g and Study FVF2587g, were designed to demonstrate the safety and efficacy of Lucentis (ranibizumab injection) in the treatment of neovascular AMD. Both study designs were prospective, multicenter, randomized, double-masked, parallel group. Study FVF2598g had an inactive control and Study FVF2587g had an approved therapy as a control.

Study FVF2598g met its primary endpoint and all of the secondary endpoints for the first treatment year. The primary endpoint was met with nearly 95% of ranibizumab-treated subjects maintaining or improving vision at 12 months, compared with 62% of sham-treated subjects ($p < 0.0001$ for each of the ranibizumab groups vs. the sham-injection group). Visual acuity results assessed at a starting test distance of 2 meters were 1-2 letters better than those assessed at a starting test distance of 4 meters. The robustness of the primary endpoint and key secondary

endpoint results was demonstrated by the consistent results from sensitivity analyses. The treatment benefit of ranibizumab on visual acuity was also consistent across the subgroups evaluated.

Study FVF2587g met its primary efficacy objective for the first treatment year. The primary efficacy objective was met with approximately 94% of subjects treated with 0.3 mg ranibizumab and 96% of subjects treated with 0.5 mg ranibizumab maintaining or improving vision at Month 12, compared with approximately 64% of verteporfin PDT–treated subjects ($p \leq 0.0001$ for superiority for each of the ranibizumab groups vs. the verteporfin PDT group). The 1-year results demonstrated a beneficial effect of ranibizumab on visual acuity. Visual acuity results based on assessment at a starting test distance of 4 meters were 1-2 letters better than those based on assessment at a starting test distance of 2 meters. The robustness of the results of the primary efficacy endpoint was demonstrated by the consistent results from sensitivity analyses. The treatment benefit of ranibizumab on visual acuity was also consistent across the subgroups evaluated.

1.3.3 Safety

The population studied was predominantly elderly and white which is representative of the population usually affected by age-related macular degeneration. The demographics of the patient population do not reflect problems with recruitment.

Based on the population studied, there does not appear to be any difference in Lucentis' effect based on age, race, ethnicity or iris color.

The most common adverse events identified are conjunctival hemorrhage, eye pain, increased intraocular pressure, retinal disorder and vitreous floaters. These adverse events are often associated with intravitreal injections.

1.3.4 Dosing Regimen and Administration

The sponsor has performed some dose ranging and dose frequency studies of Lucentis (ranibizumab injection). Lucentis (ranibizumab injection) has been proven safe and effective when administered as an intravitreal injection 0.5 mg/0.05 mL once monthly. This dosing regimen achieved and sustained a statistically significant difference in the proportion of patients who lost 15 letters of vision compared to baseline relative to the control group.

The sponsor also performed a Phase 3 trial, Study FVF3192g in which Lucentis (ranibizumab injection) was administered as an intravitreal injection 0.5 mg/0.05 mL once monthly for 3 months and then every three months. The 12-month results show that Lucentis achieved statistical significance in the primary efficacy endpoint. Study FVF3192g is reviewed in more detail in another review.

1.3.5 Drug-Drug Interactions

In Study FVF2587g, Lucentis (ranibizumab injection) was dosed with (separated by 1 week) verteporfin PDT. No drug-drug interaction analyses were performed.

1.3.6 Special Populations

There were no statistically significant differences in demographic data, diagnoses, or baseline lesion characteristics between treatment groups within each study.

Subgroup analyses did not reveal any differences in the primary efficacy endpoint with respect to age, sex, baseline visual acuity, CNV lesion type, lesion size, or prior laser photocoagulation. The safety profile was also similar in each of these groups.

The population studied for this indication was predominantly elderly and white, reflective of the population most affected by this disease. The number of patients outside of this demographic group was too small to draw any definitive conclusion regarding the safety and efficacy. There do not appear to have been any race or ethnicity effects.

No pediatric trials were conducted for this drug. Age-related macular degeneration is a disease seen only in adults.

The demographics of the patients enrolled in the trial during the development program for this product are representative of the targeted population. There is no additional data need from other populations.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	ranibizumab injection
(Proposed) Trade Name	Lucentis 0.5 mg
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection
Chemical Class	New molecular entity

Proposed Indication

adults with neovascular (wet) age-related macular degeneration

Formulation

Ingredients	Strength: Amount per 0.05 mL Vial	Function	Reference to Standard or Specification
Ranibizumab		Active ingredient	
α, α-trehalose dehydrate			
histidine HCl			Ph. Eur.
			USP and Ph. Eur.
Polysorbate 20			NF and Ph. Eur.
Water for Injection			USP and Ph. Eur.

[a] Target fill volume of per vial.

The release and shelf-life specifications for the Certificate of Analysis (C of A) testing of Lucentis Product are presented above. Shelf-life criteria for tests that are part of the stability program are only listed where they differ from the release criteria. Otherwise, the shelf-life criteria are identical to the release criteria. All release and shelf-life testing for the Lucentis Product is performed at Novartis Pharma Stein AG.

Genentech intends to use a life-cycle approach for setting ranibizumab specifications. This life-cycle approach will use interim acceptance criteria based upon the limited data available at the time of submission. Since campaign-to-campaign variation can be larger than the variation within a campaign, Genentech proposes a post-approval commitment for re-evaluating the interim acceptance criteria after three commercial post-approval campaigns (consisting of a minimum of —additional lots). The re-evaluation is expected to take place within two years after approval, but will ultimately depend on the currently unknown manufacturing schedule for ranibizumab Drug Substance.

Lucentis Drug Product Release and Shelf-Life Specifications.

Test Code	Test Name	Acceptance Criteria	Test Performed for Batch Release	Test Performed for Shelf-Life Testing
[redacted]				

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Lucentis (ranibizumab injection) is a new molecular entity and is not currently marketed in the United States nor has it been marketed or withdrawn from the market in any other country.

2.2 Currently Available Treatment for Indications

There are currently two approved drug products for the treatment of age related macular degeneration – Visudyne (verteporfin for injection) and Macugen (pegaptanib sodium injection).

Visudyne was approved under NDA 21-119 on April 12, 2000, for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration.

Macugen was approved under NDA 21-756 on December 17, 2004, for the treatment of neovascular (wet) age-related macular degeneration.

2.3 Availability of Proposed Active Ingredient in the United States

Ranibizumab is a new molecular entity and has not been marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

There have been no additional safety concerns raised with pharmacologically related products other than those discussed within this review.

2.5 Presubmission Regulatory Activity

Ranibizumab was evaluated in six clinical studies in neovascular AMD: two Phase I studies (FVF2425g and FVF1770g), two Phase I/II studies (FVF2428g and FVF2128g), and two Phase 3 studies (FVF2598g and FVF2587g).

On October 6, 1999, Genentech submitted the Investigational New Drug application (IND) for ranibizumab. Study FVF1770g was the first clinical trial performed to evaluate the safety, tolerability, pharmacokinetics, and activity of a single-dose intravitreal injection of ranibizumab. Study FVF2128g was a dose escalation study evaluating the safety, tolerability, pharmacokinetics, and activity of multidose intravitreal injections of ranibizumab. Study FVF2425g evaluated the safety, tolerability and pharmacokinetics of escalating multiple-dose intravitreal injections of ranibizumab. Study FVF2428g evaluated the safety, tolerability and efficacy of multiple-dose intravitreal injections of ranibizumab in combination with verteporfin photodynamic therapy (PDT).

A Type C Meeting was held on February 2, 2002, in which Genentech received FDA guidance on the requirements for a clinical development program to support the licensure of ranibizumab. In addition, the Agency informed Genentech that reproductive/developmental toxicology studies for bevacizumab (the full-length antibody counterpart of ranibizumab) could be cross-referenced in the Ranibizumab Biologics License Application (BLA) in lieu of conducting separate reproductive/developmental toxicology studies with ranibizumab.

On October 31, 2002 an End-of-Phase 2 Meeting was held in which Genentech presented its plans for the Phase 3 clinical program in AMD. The sponsor incorporated many, but not all of FDA recommendations into the Phase 3 protocols, including the testing of two ranibizumab dose groups (0.3 mg and 0.5 mg) in addition to a control. The most notable differences included the use of 2 meter testing instead of 4 meter testing and the use of sham injections. The Agency agreed that the BLA could be filed and reviewed based on the 1-year safety and efficacy data from each Phase 3 study; though these studies would remain masked and controlled for 2 years.

Study FVF2598g was initiated March 19, 2003. Study FVF2587g was initiated May 20, 2003. On September 21, 2005, Genentech discussed with the FDA the clinical portions of the BLA at a pre-BLA teleconference. The majority of ranibizumab studies have been sponsored by

Genentech in the United States, with the exception of Study FVF2587g, which was co-sponsored by Novartis and included sites outside of the United States, and Studies CRFB002B2201 and CRFB002A1201, which are Novartis-sponsored trials. See table in section 4.2 for a complete list of studies.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The application is approvable from a CMC perspective (see Product Review).

3.2 Animal Pharmacology/Toxicology

There were no significant findings in the pharmacology/toxicology reviews which would affect the clinical outcome.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on the results of the applicant supported trials for AMD conducted under BBIND —. Phase 3 safety and efficacy trials were submitted to support the indication currently being sought by the applicant. In addition, the results of four phase 1/2 dose ranging and safety trials were also submitted.

This NDA was submitted in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

4.2 Tables of Clinical Studies

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Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
PIVOTAL PHASE 3 TRIALS								
FVF2587g [redacted]	3	Randomized, double-masked, double-sham,[a] active treatment-controlled (US, Europe, Australia)	Subjects with predominantly classic subfoveal neovascular AMD	Verteporfin PDT (+sham injection)	423	Intravitreal injection q month, max. 24 injxns over 2 yrs, or verteporfin PDT q3mos as needed	0.3 mg (n=140), 0.5 mg (n=140), sham injection (n=143)	**Ongoing**[b]
FVF2598g [redacted]	3	Randomized, double-masked, sham-controlled (US)	Subjects with minimally classic or occult subfoveal neovascular AMD	Sham injection	716	Intravitreal injection q mo., max. 24 injxns over 2 years	0.3 mg (n=238), 0.5 mg (n=240), sham injection (n-238)	**Ongoing**[b]
ADDITIONAL PHASE 3 TRIALS								
FVF3192g [redacted]	3b	Randomized, double-masked, sham-controlled (US)	Subjects with recurrent subfoveal CNV with or without classic CNV secondary to AMD	Sham injection	184	Intravitreal injection q month for 3 doses (Day 0, Month 1, Month 2) followed by doses q 3 months (Mos. 5, 8, 11, 14,	0.3 mg 0.5 mg sham injection (Target: 61-62 subjects per group)	Ongoing

Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
						17, 20 and 23)		
FVF2508g	Extension	Extension (US)	Subjects with neovascular AMD who completed a Genentech Phase 1/2 ranibizumab study	None	70	Intravitreal injections every 28 days (± 5 days) through October 2006 or until 30 days after product launch	0.5 mg (n=66)	Ongoing
FVF3426g [redacted]	Extension	Extension, open-label (US)	Subjects with subfoveal CNV secondary to AMD who completed a Genentech ranibizumab study	Ranibizumab naïve	Target 600	Intravitreal injections q 30 days for up to 24 months or until 30 days after product launch	0.5 mg (Target: 600 subjects)	Ongoing

a The active ranibizumab groups also received sham PDT with saline infusions, and the verteporfin PDT group received sham intravitreal injections.
b Enrollment has been completed; the study is ongoing.
c Excludes 5 subjects in Study FVF2128g and 3 subjects in Study FVF2425g who were enrolled but discontinued from the study before Day 0.
d Standard of care as determined by the treating physician and/or investigator.
e Novartis sponsored study.

Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
PHASE 1 / 2 DOSE RANGING TRIALS								
FVF2425g	1	Randomized, open-label, multiple-dose escalating regimens (US)	Subjects with neovascular AMD	None	29[c]	Intravitreal injections at 2- or 4-week intervals, max. of 5, 7 or 9 total injections over 16 weeks	0.3 mg to 1.0 mg escalating regimen with 7 total injxns (n=9); 0.3mg to 2.0 mg escalating regimen with 9 total injxns (n=10); 0.3 mg to 2.0 mg escalating regimen with 5 total injxns (n=10)	Completed
FVF2128g	1/2	Randomized, open-label, dose-escalation (US)	subjects with classic neovascular AMD	Usual care[d]	64[c]	Intravitreal injections q 4 weeks, maximum of 8 total injections over 28 weeks, or usual care with crossover to ranibizumab treatment after 14 weeks	0.3 mg (n=25), 0.3 mg initial dose escalated to 0.5 mg for subsequent doses 9n=28), usual care (n=11)	Completed
FVF1770g	1	Open-label, single-dose escalation (US)	Subjects with neovascular AMD	None	27	Single intravitreal injection	0.05 mg (n=6), 0.15 mg (n=6), 0.30 mg (n=6), 0.50 mg (n=7), 1.0 mg (n=2)	Completed

Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
FVF2428g	1/2	Randomized, single-masked, sham-controlled, combination treatment (US)	Subjects with predominantly classic neovascular AMD	Verteporfin PDT (+sham injection)	162	Intravitreal injection qmonth, max. 24 injxns over 2 years, in combination with verteporfin PDT q3mos, as needed	0.5 mg (n=106), sham injection (n=56)	Ongoing[b]
NOVARTIS SPONSORED TRIALS								
CRFB002A1201[c]	1/2	Open-label (Japan)	Subjects with subfoveal CNV secondary to AMD	None	Target 84	Intravitreal injections every month	0.3 mg 0.5 mg (Target: 42 subjects per group)	Ongoing
CRFB002B2201[c]	2	Open-label (Europe)	Subjects with occult or predominantly classic subfoveal CNV secondary to AMD	Verteporfin PDT	32	Intravitreal injections every month in combination with verteporfin PDT	0.5 mg (n=30)	Ongoing

4.3 Review Strategy

This review evaluates the results of two Phase 3 trials submitted by the applicant. Each individual study was evaluated in depth to determine if the data supported the primary efficacy endpoint. The integrated safety and efficacy database was finally evaluated to determine the overall risk/benefit profile for this drug product.

The submitted clinical study reports, clinical protocols and literature reports related to trials FVF2598g and FVF2587g were reviewed. The application is in electronic format as a hybrid CTD (i.e., CTD structure with PDF tables of contents), according to ICH and FDA guidelines for electronic submissions.

4.4 Data Quality and Integrity

There is no evidence that Phase 3 studies reviewed in this BLA were not conducted in accordance with acceptable clinical ethical standards.

There were no new Division of Scientific Investigations (DSI) audits completed by the time of this review. The case report forms for the three studies were provided by Genentech, and these were reviewed for completeness and quality.

Several investigators who participated in Study FVF2598g and FVF2587g were inspected by DSI within the past 24 months. [redacted], was inspected in August 2004 and given a final classification of VAI. [redacted] was inspected in March 2005 and given a final classification of NAI.

4.5 Compliance ~~with~~ Good Clinical Practices

The studies were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practice (GCPs), the Declaration of Helsinki and in compliance with relevant local and national regulations for informed consent and protection of subject rights in the country of conduct.

Before initiation of the study, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The studies began only after receiving written approval from each EC/IRB.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence suggesting problems with the integrity of the submitted data.

5 CLINICAL PHARMACOLOGY

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.

5.1 Pharmacokinetics

Ranibizumab is administered intravitreally for the treatment of neovascular AMD and subsequently absorbed into the systemic circulation. Attempts were made to measure systemic pharmacokinetics from serum samples. Elimination of ranibizumab from systemic circulation is believed to be absorption rate limited based on nonclinical pharmacokinetic data. In the noncompartmental pharmacokinetic analysis of serum concentration data from 10 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 pharmacokinetics over the dose range studied. Results from these 10 subjects also indicated that ranibizumab serum concentrations following a single intravitreal ranibizumab dose of 0.3–1.0 mg/eye were lower than the concentration range of ranibizumab expected to reduce VEGF-induced endothelial cell proliferation by 50% (IC_{50}); 0.23– 0.56 nM, which is equivalent to 11–27 ng/mL, based on a molecular mass of 48 kDa for ranibizumab.

A population pharmacokinetic analysis (Study 05-1181) was conducted to summarize data obtained from five ranibizumab clinical studies: four studies in which ranibizumab was used as a single agent (Studies FVF1770g, FVF2128g, FVF2425g, and FVF2598g) and one study in which ranibizumab was administered to subjects concomitantly with verteporfin PDT (Study FVF2428g). This analysis included a total of 675 measurable ranibizumab samples 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 2 weeks to every month. In all studies, ranibizumab was administered intravitreally as a bolus to one study eye. Based on the final model, several covariates were correlated with population pharmacokinetic parameter estimates. Serum creatinine clearance (CrCL) was found to be the most significant covariate for apparent systemic clearance (CL/F) of ranibizumab. However, when compared with the large intersubject variability of CL/F, the effect of CrCL on CL/F was determined to have no clinical significance. Verteporfin PDT was found to decrease the elimination rate of ranibizumab from the eye. Although this finding is consistent with expected anatomical changes of a lesion following verteporfin PDT, it has no effect on ranibizumab systemic exposure. For a typical

subject, the CL/*F* was 23.8 L/day, the apparent volume of the central compartment was 2.97 L, and the elimination rate of ranibizumab was 0.0800 day $^{-1}$. In summary, there is no covariate that affects the systemic exposure of ranibizumab with clinical significance.

5.2 Pharmacodynamics

In vitro, maximal inhibition of rhVEGF-induced proliferation of human umblical vein endothelial cells was observed at ranibizumab concentrations of approximately 1.29 nM (which is equivalent to 62 ng/mL assuming a molecular weight for ranibizumab of 48 kDa). The population pharmacokinetic model for predicted minimum vitreal ranibizumab concentration with a monthly dosing regimen of 0.3-mg ranibizumab is 12 µg/mL (range, 2.3–41 µg/mL) and above the concentrations necessary to inhibit VEGF activity.

In vivo, neovascular AMD may be associated with foveal retinal thickening as assessed by optical coherence tomography (OCT) and leakage from CNV as assessed by fluoresceinangiography.

Foveal retinal thickness was assessed using OCT in a subset of subjects in Study FVF2598g (46 of 716 subjects with a baseline evaluation) and Study FVF2587g (53 of 423 subjects with a baseline evaluation). In subjects treated with ranibizumab (pooled data from the 0.3-mg and 0.5-mg groups), on average, foveal retinal thickness decreased by Day 7 and continued to decrease through Month 12. On Day 7, the average change in Study FVF2598g was − 84 µm for ranibizumab compared with − 23 µm for the sham-injection control ($p = 0.099$). In Study FVF2587g, the average change was − 105 µm for ranibizumab compared with − 26 µm for verteporfin PDT ($p = 0.008$). At Month 12, the average change in Study FVF2598g was − 123 µm for ranibizumab compared with − 15 µm for sham-injection control ($p = 0.009$). In Study FVF2587g, the average change was − 190 µm for ranibizumab compared with − 87 µm for verteporfin PDT ($p = 0.0004$).

In subjects treated with monthly injections of ranibizumab in Studies FVF2598g and FVF2587g, the area of leakage from CNV as assessed by fluorescein angiography decreased, on average, by Month 3. In Study FVF2598g, the average change was approximately − 1.0 disc areas (DA) for subjects in both the 0.3-mg and 0.5-mg 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 0.3-mg and 0.5-mg ranibizumab groups compared with + 0.2 DA for subjects in the verteporfin PDT group ($p < 0.0001$). However, it is known that the area of leakage from CNV does not correlate with visual function.

5.3 Exposure-Response Relationships

The retina is the site of disease in neovascular AMD. Therefore, systemic ranibizumab concentrations after intravitreal administration are not expected to correlate with efficacy.

Ranibizumab systemic pharmacokinetics were characterized throughout the clinical program, including a population pharmacokinetic analysis.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is [redacted] in patients with neovascular (wet) age-related macular degeneration.

6.1.1 Methods

The submitted Phase 3 studies (FVF2598g and FVF2587g) were reviewed independently to determine if the results of each trial demonstrated efficacy for the primary efficacy endpoint. The primary efficacy endpoint for each trial was a responder analysis of the proportion of patients who lost fewer than 15 letters of visual acuity from baseline (doubling of the visual angle) at 54 weeks. This analysis was done for two populations which represent different ranges of data to evaluate the robustness of the results; an all randomized patient population with last-observation-carried-forward (LOCF) and the per protocol population with observed cases only.

6.1.2 General Discussion of Endpoints

Visual acuity is a well-established and validated measure of visual function that has been used for decades in ophthalmology research. The methods used in this study follow methods used in clinical trials of both diabetic macular edema and AMD.

Reviewer's Comment:

In choroidal neovascularization secondary to age-related macular degeneration, a recommended endpoint is a statistically significant difference between groups in the percentage of patients with a halving of the visual angle (15 letters or more on an Early Treatment Diabetic Retinopathy visual acuity chart measured at 4 meters).

6.1.3 Study Design

6.1.3.1 Study FVF2598g

Title: A Phase 3, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of rhuFab V2 (Ranibizumab) in Subjects with Minimally Classic or Occult Subfoveal Neovascular Age-Related Macular Degeneration.

Objectives: Primary:

- To evaluate the efficacy of intravitreal injections of ranibizumab (0.3 mg and 0.5mg) 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
- To evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly

Secondary:

- To evaluate the efficacy of monthly intravitreal injections of ranibizumab in preventing vision loss as measured by the following:
  - The mean change from baseline in visual acuity over time up to 12 months
  - The proportion of subjects who gained at least 15 letters in visual acuity at 12 months compared with baseline
  - The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 12 months
- To investigate the efficacy of monthly intravitreal injections of ranibizumab on vision-related functioning and well being assessed during a period of 12 months, as measured by the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25)
- To evaluate the efficacy of monthly intravitreal injections of ranibizumab on the size of CNV and amount of leakage from CNV at 12 months, as assessed by fluorescein angiography

Study Design: This is a prospective, multicenter (96 sites), randomized, double-masked, sham injection-controlled trial of intravitreally administered ranibizumab.

Test Drug Schedule:

Eligible subjects were randomized in a 1:1:1 ratio to receive 0.5 mg ranibizumab, 0.3 mg ranibizumab or sham injection. Subjects received a ranibizumab or sham injection monthly (30 ± 7 days) for up to a maximum of 13 injections during the first treatment year (Day 0 to Month 12). The second treatment year of the study is ongoing. Subjects have continued to receive monthly ranibizumab or sham injections during the second treatment year with the last injection administered at Month 23. Subjects will have a final safety visit at Month 24.

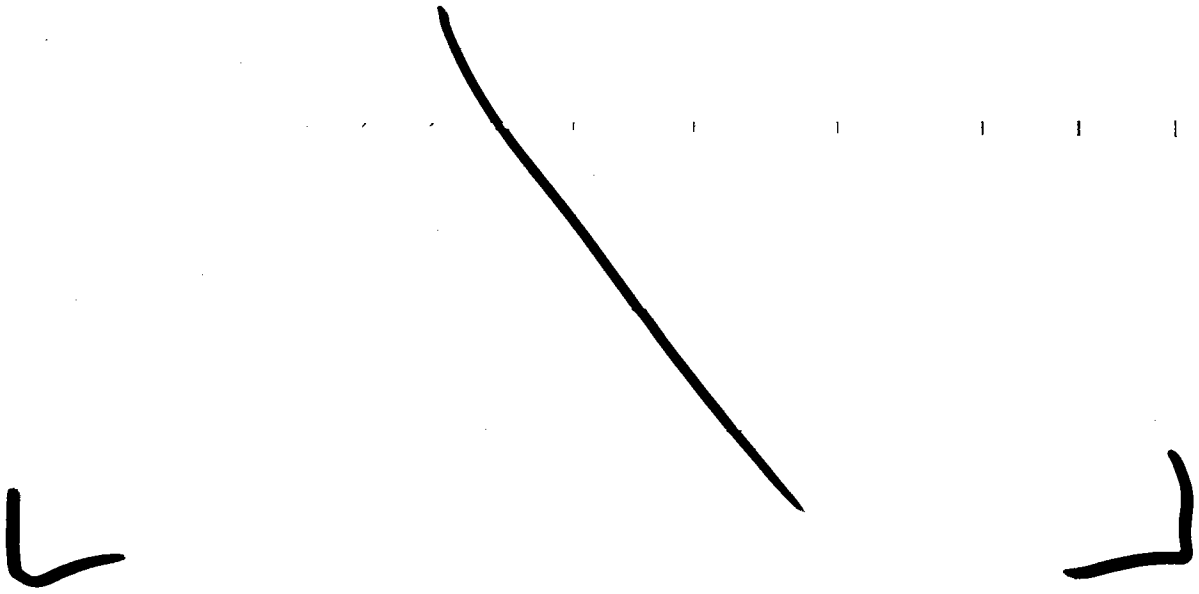
7 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 4076



Study Design

This was a Phase 3, multicenter, randomized, double-masked, sham injection–controlled study of intravitreally administered ranibizumab. Approximately 720 subjects with primary or recurrent subfoveal CNV secondary to AMD who have minimally classic or occult lesions were enrolled.

Consented subjects participated in a screening period lasting up to 28 days to determine eligibility. Fluorescein angiograms were sent to a central reading center to determine CNV classification for study eligibility. Eligible subjects were randomized in a 1:1:1 ratio to receive 0.5 mg of ranibizumab, 0.3 mg of ranibizumab, or a sham injection. Randomization was stratified by the visual acuity score at Day 0 ($\leq$ 54 letters [approximately worse than 20/80] vs. $\geq$ 55 letters [approximately 20/80 or better] based on the ETDRS chart and assessment at a starting distance of 2 meters), by type of CNV (minimally classic CNV vs. occult CNV without classic component), and by study center. A dynamic randomization scheme was used to obtain approximately a 1:1:1 ratio among the treatment groups. Subjects received a ranibizumab or sham injection monthly for 23 months of treatment (24 injections). Only one eye was chosen as the "study eye." Only the study eye received intravitreal injections of ranibizumab or a sham injection.

After careful review of data, including 12-month data from this ongoing study, Genentech believed that it was in the best interest of subjects randomized to the sham-injection group to

cross over to receive ranibizumab. Specifically, subjects randomized to the sham-injection group who had not completed their Month 23 visit (last possible injection visit) would cross over to receive monthly injections of 0.5 mg ranibizumab for the remainder of the treatment period upon approval of the current protocol amendment (dated 9 September 2005) and Informed Consent Form by the site Institutional Review Board (IRB). Subjects who had discontinued the study and/or treatment were excluded from the crossover.

A minimum of two investigators per study site was required to fulfill the masking requirements of this study. At least one investigator was designated the evaluating physician, who was masked to the treatment assignment and conducted all ocular assessments. At least one other investigator was designated the injecting physician, who was unmasked to the treatment assignment and performed the ranibizumab/sham preparation, but was masked to study drug dose (0.3 mg vs. 0.5 mg of ranibizumab). Once the designated roles were determined, the roles could not be switched at any time during the conduct of the study. The injecting physicians (and designated unmasked assistants, if needed) were not permitted to be involved in the conduct of the study in any other manner and could not communicate with any other personnel or subjects regarding the treatment assignment.

Subjects had scheduled monthly visits throughout the study for the evaluation of safety and efficacy. Subjects had either the first injection of intravitreal ranibizumab or a sham injection by the injecting physician on Day 0 and underwent safety and eye assessments by the evaluating physician (e.g., indirect ophthalmoscopy and slit lamp examination) 7 days after the first injection. At subsequent visits (every month), the subject had a safety evaluation by the evaluating physician prior to study drug injection. The monthly visits were scheduled every 30 days relative to Day 0. Subjects were contacted by the site personnel 2 days after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they had taken the prescribed self-administered post-injection antimicrobials. Subjects will have a final safety visit at Month 24.

Study Treatment

Ranibizumab was administered in a multiple-dose regimen of either 0.3 mg or 0.5 mg of ranibizumab every month (Day 0-Month 23) for a total of 24 injections. Sham injections were given monthly or until the subjects crossed over, and then 0.5 mg ranibizumab was to be administered monthly during the crossover period for the remainder of the treatment period. The cross over was to be implemented upon approval of the current protocol amendment and Informed Consent Form by the site's IRB. If verteporfin PDT had been given in the study eye within the last 28 days, then the ranibizumab/sham injection was held.

Study Population
Inclusion Criteria

Subjects had to meet the following inclusion criteria to be eligible for study entry:

1. Age $\geq$ 50 years
2. Active primary or recurrent subfoveal CNV lesions secondary to AMD in the study eye, as defined in the following table.

Table 6.1.3.1-2 - Definitions of Terms Pertaining to AMD Inclusion Criteria

Term	Definition
Active	Any of the following: 1) Exhibiting a ≥ 10% increase in lesion size, as determined by comparing a fluorescein angiogram performed within 1 month preceding Day 0, inclusive, with a fluorescein angiogram performed within 6 months preceding Day 0, inclusive; or 2) Resulting in a visual-acuity loss of ≥ 1 Snellen line (or equivalent) and occurring at any time within the prior 6 months; or 3) Subretinal hemorrhage associated with CNV within 1 month preceding Day 0
Primary	Newly diagnosed and previously untreated
Recurrent	Previously diagnosed and regressed but currently presenting with a new, active component
Subfoveal	Including the center of the fovea within the boundaries of the CNV
CNV lesion	A contiguous area of abnormal tissue in the macula that encompasses angiographically documented CNV with possible additional components of subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and fibrosis
AMD	Clinical and/or angiographic signs consistent with AMD (e.g., drusen, retinal pigment epithelial changes, choroidal neovascularization) with no other likely etiologic explanations for the degenerative changes

3. Lesions with occult CNV or with some classic CNV component were permissible. However, if classic CNV (well-demarcated hyperfluorescence boundaries in the early phase of the fluorescein angiogram) was present, the area of classic CNV had to be < 50% of the total lesion size.
4. Total area of CNV (including both classic and occult components) encompassed within the lesion ≥ 50% of the total lesion area.
5. Total lesion area ≤ 12 disc areas (DA) in size
6. Best corrected visual acuity, using ETDRS charts, of 20/40 to 20/320 (Snellen equivalent) in the study eye

   Only one eye was assessed in the study. If both eyes were eligible, the one with the better visual acuity was selected for treatment and study unless, based on medical reasons, the investigator deemed the other eye the more appropriate candidate for treatment and study.

Exclusion Criteria

Subjects who met any of the following exclusion criteria were ineligible for study entry:

a. Prior/Concomitant Treatment

1. Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy (TTT) in the study eye
2. Treatment with verteporfin in the non-study (fellow) eye less than 7 days preceding Day 0
3. Previous participation in a clinical trial (for either eye) involving anti-angiogenic drugs (Pegaptanib, Ranibizumab, anecortave acetate, protein kinase C inhibitors, etc.)

4. Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation) in the study eye
5. Previous subfoveal focal laser photocoagulation in the study eye
6. Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within 1 month preceding Day 0
7. History of vitrectomy surgery in the study eye
8. History of submacular surgery or other surgical intervention for AMD in the study eye
9. Previous participation in any studies of investigational drugs within 1 month preceding Day 0 (excluding vitamins and minerals)

b. Lesion Characteristics

1. Subretinal hemorrhage in the study eye that involved the center of the fovea, if the size of the hemorrhage was either ≥ 50% of the total lesion area or ≥ 1 DA in size.
2. Subfoveal fibrosis or atrophy in the study eye
3. CNV in either eye due to other causes, such as ocular histoplasmosis, trauma or pathologic myopia
4. Retinal pigment epithelial tear that involved the macula in the study eye

c. Concurrent Ocular Conditions

1. Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, either
   i. Required medical or surgical intervention during the 24-month study period to prevent or treat visual loss that may have resulted from that condition, or
   ii. If allowed to progress untreated, could likely have contributed to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 24-month study period
2. Active intraocular inflammation (grade trace or above) in the study eye
3. Current vitreous hemorrhage in the study eye
4. History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
5. History of idiopathic or autoimmune-associated uveitis in either eye
6. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
7. Aphakia or absence of the posterior capsule in the study eye
   i. Previous violation of the posterior capsule in the study eye was also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation.
8. Spherical equivalent of the refractive error in the study eye that demonstrated more than -8 diopters of myopia
9. Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding Day 0
10. Uncontrolled glaucoma in the study eye (defined as intraocular pressure [IOP] ≥ 30 mmHg despite treatment with anti-glaucoma medication)
11. History of glaucoma filtering surgery in the study eye
12. History of corneal transplant in the study eye

d. Concurrent Systemic Conditions

1. Pre-menopausal women not using adequate contraception
    i. The following were considered effective means of contraception: surgical sterilization; use of oral contraceptives; barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel; an intrauterine device; or contraceptive hormone implant or patch
2. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug or that might have affected interpretation of the results of the study or rendered the subject at high risk for treatment complications
3. Current treatment for active systemic infection

e. Other

1. History of allergy to fluorescein, not amenable to treatment
2. Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded by the central reading center
3. Inability to comply with study or follow-up procedures

Outcome Measures

Primary Efficacy Outcome Measures

The proportion of subjects who lost fewer than 15 letters (approximately 3 lines) in the best corrected visual acuity score at 12 months compared with baseline, based on the ETDRS visual acuity chart and assessment at a starting distance of 2 meters.

Secondary Efficacy Outcome Measures – For the First Treatment Year

- Proportion of subjects who lost fewer than 15 letters in the best corrected visual acuity score at 12 months compared with baseline, based on assessment at a starting test distance of 4 meters
- Mean change from baseline in the best corrected visual acuity score over time up to 12 months
- Proportion of subjects who gained at least 15 letters in the best corrected visual acuity score at 12 months compared with baseline
- Proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 12 months (legal blindness is defined as both eyes with 20/200 or worse)
- Mean change from baseline in the VFQ-25 near activities subscale score over time up to 12 months
- Mean change from baseline in the VFQ-25 distance activities subscale score over time up to 12 months
- Mean change from baseline in the VFQ-25 vision-specific dependency subscale score over time up to 12 months
- Mean change from baseline in the total area of CNV at 12 months (based on assessment by the central reading center)
- Mean change from baseline in the total area of leakage from CNV at 12 months (based on assessment by the central reading center)

The secondary efficacy outcome measures for the second treatment year of the study are the following:

- Proportion of subjects who lose fewer than 15 letters in the best corrected visual acuity score at 24 months compared with baseline
- Mean change from baseline in the best corrected visual acuity score at 24 months
- Proportion of subjects who gain at least 15 letters in the best corrected visual acuity score at 24 months compared with baseline
- Proportion of subjects with a visual-acuity Snellen equivalent of 20/200 or worse at 24 months
- Proportion of subjects who lose fewer than 15 letters in the best corrected visual acuity score at 24 months compared with baseline, based on assessment at a starting test distance of 4 meters
- Mean change from baseline in the VFQ-25 near activities subscale at 24 months
- Mean change from baseline in the VFQ-25 distance activities subscale at 24 months
- Mean change from baseline in the VFQ-25 vision-specific dependency subscale at 24 months
- Mean change from baseline in the total area of CNV at 24 months (based on assessment by the central reading center)
- Mean change from baseline in the total area of leakage from CNV at 24 months (based on assessment by the central reading center)

Safety Outcome Measures

The safety outcome measures are the following:

- The incidence and severity of ocular adverse events
- The incidence and severity of non-ocular adverse events
- Changes and abnormalities in clinical laboratory parameters
- The incidence of serum antibodies to ranibizumab
- Changes in vital signs

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint.

Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters, not 2 meters, from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters, not 2 meters.

The VFQ-25 scale and its subscales have not been validated against actual activities of daily living.

SAFETY PLAN

Following each injection (ranibizumab or sham), subjects were to remain at the clinic for at least 60 minutes (± 10 minutes). Finger counting was tested on each subject after each injection; hand motion and light perception was tested when necessary. Intraocular pressure was measured before and 60 minutes (± 10 minutes) after each injection. If there were no safety concerns in the 60 minutes (± 10 minutes) following an injection, the subject was to leave the clinic. If any concern or immediate toxicity was noted, the subject was to remain at the clinic and be treated according to the designated evaluating physician's clinical judgment.

Subjects were to return for a follow-up visit at Day 7 after the first injection. In addition, subjects were to be contacted by study site personnel 2 days (± 1 day) after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they have taken the prescribed self-administered post-injection antimicrobials. If determined necessary by the evaluating physician, the subject was asked to return to the clinic as soon as possible for a safety assessment visit and was evaluated by the designated evaluating physician. Subjects were instructed to contact their designated evaluating physician at any time should they have health-related concerns.

Detailed ocular examinations, including indirect ophthalmoscopy, measurement of intraocular pressure, visual acuity testing, and slit lamp examination, was performed throughout the study by the designated evaluating physician. Routine hematology, chemistry, and urinalysis profiles were obtained for all subjects. In addition, blood samples for serum ranibizumab concentrations and antibodies to ranibizumab were obtained for all subjects.

Study drug administration was temporarily held for subjects who experience certain ocular events or infection events. Study drug administration was also held at a visit if the evaluating physician suspected that the lesion in the study eye had converted to predominantly classic CNV and verteporfin PDT treatment was being considered. In the event any subject developed an adverse event in the study eye that was considered by the designated evaluating physician to be severe in intensity, serious consideration was to be given to discontinuing the subject from study treatment. The investigator or Sponsor could request that a subject be withdrawn from treatment or from the study for safety reasons at any time.

Subjects who were discontinued from study treatment were to continue to undergo the scheduled monthly assessments. Subjects withdrawn from the study prior to completion were asked to return for an early termination evaluation 30 days (± 7 days) following their last injection/study visit for monitoring of all adverse events (serious and nonserious; ocular and non-ocular).

Preliminary findings from FVF2428g (see Section 1.7.4) suggest that administering the ranibizumab injections 7 days (± 2 days) after treatment with verteporfin PDT in the same eye might result in a decrease in visual acuity of ≥ 30 letters due to temporary intraocular inflammation (uveitis). Therefore, if verteporfin PDT treatment was required in the study eye, it was to be administered at least 28 days prior to ranibizumab/sham injections and no sooner than 21 days after ranibizumab/sham injections.

A formal Data Monitoring Committee (DMC) was established to monitor subject safety. The DMC conducted semiannual reviews of unmasked safety data including serious adverse events, adverse events (ocular and non-ocular), deaths, clinically significant decreases in visual acuity, and results of ocular assessments.

Concomitant Therapy and Clinical Practice

Subjects who received prior treatment with verteporfin in the study eye were excluded from the study. Verteporfin therapy in the non-study eye less than 7 days prior to Day 0 was not permitted.

Subjects who are confirmed (by fluorescein angiography and written documentation) by the central reading center to have changed lesion classification from minimally classic/occult CNV to predominantly classic CNV could receive alternative therapies (e.g., verteporfin) in the study eye.

Pegaptanib sodium injection was not permitted in either eye due to the potential safety concern of concurrent treatment with two anti-VEGF agents.

Concurrent use of systemic anti-VEGF agents including treatment with intravitreal or intravenous Avastin was not permitted in either eye. Subfoveal laser photocoagulation in the study eye was not allowed prior to Day 0 or during study participation. Juxtafoveal or extrafoveal laser photocoagulation for AMD was not allowed in the study eye within 1 month preceding Day 0 and during study participation. Elective vitrectomy surgery was not allowed in the study eye during study participation. Transpupillary thermotherapy (TTT), external beam radiation therapy, submacular surgery, or other surgical intervention for AMD was not allowed in the study eye during study participation. Onset of glaucoma during study participation should be treated as clinically indicated. Cataract surgery in the study eye could be performed if clinically indicated and should occur ≥ 28 days after the last ranibizumab or sham injection; the next ranibizumab or sham injection will be held for ≥ 28 days following cataract surgery. At least one monthly injection was to be missed when cataract surgery in the study eye is performed.

Dose Holding and Treatment Discontinuation

Dose interruption and treatment discontinuation due to adverse events were determined using the criteria in the following Table. If any of the listed events occurred, the reason for dose holding was recorded on the Study Drug Administration Case Report Form (CRF) and, if applicable, on the Adverse Event CRF.

Table 6.1.3.1-3 Dose Holding and Treatment Discontinuation Criteria

Event	Study Drug Dose Holding Criteria
Intraocular inflammation	Dose was held if intraocular inflammation was ≥ 2+ in the study eye.
Visual acuity loss	Dose was held if there was a treatment-related decrease in best corrected visual acuity of ≥ 30 letters in the study eye compared with the last assessment of visual acuity prior to the most recent treatment.

Intraocular pressure	Dose was held if IOP in the study eye was ≥ 30 mmHg. Treatment was permitted when IOP had been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the evaluating physician.
Vitreous hemorrhage	Dose was held if there was a ≥ 2+ vitreous hemorrhage and ≥ 30-letter decrease in visual acuity in the study eye compared with the last assessment of visual acuity prior to the onset of the vitreous hemorrhage. Treatment was permitted when the vitreous hemorrhage improved to <2+ or visual acuity score improved to a <30-letter decrease.
Sensory rhegmatogenous retinal break or detachment (including macular hole)	Dose was held if a retinal break was present in the study eye. Treatment may have been resumed ≥ 28 days after the retinal break had been successfully treated. Subjects with a rhegmatogenous retinal detachment or Stage 3 or 4 macular hole were discontinued from treatment for the duration of the study.
Subfoveal hemorrhage	Dose was if there was a subretinal hemorrhage involving the center of the fovea in the study eye, if the size of the hemorrhage was either ≥ 50% of the total lesion area or ≥ 2 DAs in size.
Local or systemic infection	Dose was held if any of the following were present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye, or if the subject was receiving treatment for a severe systemic infection.
Intraocular surgery	Dose was held if intraocular surgery had been performed in the study eye within the previous 28 days.

Analysis Populations

Randomized Subjects

These subjects were enrolled and randomized in the study. This population was used for summaries of demographics and study conduct and for most summaries of efficacy. Treatment group assignment for this population was as randomized (i.e., ITT).

Per Protocol Subjects

A subset of randomized subjects who were considered more compliant with the protocol. Treatment group assignment for this population was as randomized. This population was used for supportive analyses of visual acuity efficacy outcome measures at Month 12.

Safety Evaluable Subjects

Randomized subjects who received at least one treatment with study drug. Treatment group assignment for this population was defined as follows:

- Sham: subjects randomized to the sham-injection group who received a sham injection on Day 0
- 0.3 mg Ranibizumab: subjects randomized to receive 0.3 mg ranibizumab or subjects who were randomized to sham but received a 0.3 mg injection of ranibizumab on Day 0 in error
- 0.5 mg Ranibizumab: subjects randomized to receive 0.5 mg ranibizumab or subjects who were randomized to sham but received a 0.5 mg injection of ranibizumab on Day 0 in error.

Efficacy Analyses

Comparisons of efficacy were performed between each ranibizumab dose group and the sham injection (control) group. All pairwise comparisons for treatment difference were performed using a statistical model that included only two treatment groups (active vs. control) at a time. For the primary efficacy endpoint, an adjustment was made for multiple treatment comparisons of each ranibizumab dose group with the control group. For secondary efficacy endpoints, adjustments for multiplicity of endpoints were made to manage the Type I error.

Primary Efficacy Endpoint. The proportion of subjects with fewer than 15 letters lost in best corrected visual acuity at 12 months compared with baseline, based on assessment at a starting test distance of 2 meters, was compared between each ranibizumab group and the sham control group using the Cochran $\chi 2$ test stratified by CNV classification at baseline and baseline visual acuity score. The test was performed at an overall significance level of 0.0497 after adjusting for interim analyses. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for the two pairwise treatment comparisons. If the p-values for both comparisons were 0.0497, both ranibizumab groups were considered statistically significantly different from the sham control group. If the p-value for the comparison of one ranibizumab group with the sham control group was $p > 0.0497$, the other ranibizumab group was considered statistically significantly different from the control group only if the p-value for its comparison with the control group was 0.0497/2 (0.02485). Results of tests for treatment difference using the Cochran $\chi 2$ test stratified by the baseline visual acuity score and CNV classification entered into the IVRS at randomization were also provided as supportive analyses.

Reviewer's Comments:

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters, not 2 meters.

Determination of Sample Size

The sample size of 720 subjects with minimally classic or occult CNV will provide 95% power in the intent-to-treat (ITT) analysis to detect a statistically significant difference between one or both ranibizumab groups and the control group in the percentage of subjects with fewer than 15 letters lost at Month 12, assuming a rate of 65% in each ranibizumab group and 50% in the control group.

Interim Analyses

An independent DMC was established to monitor safety and study conduct and met approximately every 6 months to review unmasked safety summaries prepared by an external statistical coordinating center. Because the analyses involve visual acuity, which is the basis of the primary efficacy endpoint, each interim analysis conducted prior to the analysis of the primary efficacy endpoint will be allocated a Type I error of $\alpha=0.0001$.

Table 6.1.3.1-4
Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

Study Period	Screen	Treatment Phase														Early Term
	Day			Month												
	-28 to -1	0	7	1	2	3	4	5	6	7	8	9	10	11	12	
Assessment Window (Days)	—	—	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	[illegible]
Informed Consent	x															
Inclusion/Exclusion Criteria	x															
Demographic data	x															
Medical and surgical history	x															
VFQ-25 [c]		x		x	x	x			x			x			x	x
SF-36 Health Survey [c]		x							x						x	x
HUI (at selected sites only) [c]	x	x				x				x			x			x
VAS [c]	x			x	x	x				x			x			x
Review of Body Systems	x														x	x
Serum pregnancy test [d]	x															
Best corrected visual acuity (2 meter starting distance) [e, f]	x	x [g]	x	x	x	x	x	x	x	x	x	x	x	x	x [g]	x [g]
Slit Lamp Examination [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect and high-magnification ophthalmoscopy [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lens status assessment		x													x	
Fundus Photography [e]	x					x			x						x	x
Fluorescein Angiography [e]	x					x			x						x	x
Contrast Sensitivity [e, f]	x		x	x	x	x			x						x	x
OCT (at selected sites) [e]		x	x	x											x	x
Laboratory Samples [e, h]	x														x	x
Serum samples for antibodies to ranibizumab and ranibizumab concentrations [e]	x								x						x	x
Intraocular pressure [i, j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ranibizumab administration or sham injection (study eye only)		x		x	x	x	x	x	x	x	x	x	x	x	x	
Finger count, hand motion, light		x		x	x	x	x	x	x	x	x	x	x	x	x	

Study Period	Screen	Treatment Phase														Early Term.[a]
	Day			Month												
	-28 to -1	0	7	1	2	3	4	5	6	7	8	9	10	11	12	
Assessment Window (Days)	—	—	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	30±7
perception [k]																
Vital Signs [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events [e, l, n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact [o]		x		x	x	x	x	x	x	x	x	x	x	x	x	

Note: Except as noted, all ocular assessments were to be performed on both eyes. For study drug treatment visits, all assessments must have been performed on the same day as study drug treatment.

a For subjects who withdrew from the study early. Performed 30 days (±7 days) following the last injection or study visit.
b Significant medical/surgical history, including chronic and ongoing conditions (e.g., trauma, cancer history, and ophthalmic history).
c VFQ-25 , SF-36 Health Survey, HUI questionnaire (selected sites only), and VAS should have been administered to the subject prior to the subject's completing any other study procedures.
d For women of childbearing potential.
e Performed pre-injection.
f Performed prior to dilating eyes.
g Also assessed at a starting distance of 4 meters after assessment at a starting distance of 2 meters.
h Laboratory evaluations included hematology, blood chemistry, and urinalysis
i Obtained pre-injection for both eyes and 60 minutes (±10 minutes) post injection for study eye only
j The measurement method used for a subject was to remain consistent throughout the study.
k Injecting physician was to perform within 15 minutes post-injection for study eye only.
l Performed post-injection
m Any prescription drugs or OTC preparations other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes, etc.) and pre- and post-injection medications (e.g., proparacaine, antimicrobials) used by a subject within 7 days preceding Day 0.
n Adverse events were collected from Day o through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab were followed, even after the subject's study participation was over, until the event resolved or the event was assessed as irreversible, chronic, or stable.
o Subjects were contacted 2 days (1 day) following treatment to elicit reports of any decreases in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they had taken the prescribed post-injection antimicrobials.

Table 6.1.3.1-5 Subject Disposition

	Number of Subjects			
	Sham Injection N (%)	Ranibizumab 0.5 mg N (%)	Ranibizumab 0.3 mg N (%)	Total N (%)
Randomized	238	238	240	716
Completed Month 12 [a]	212 (89.1%)	226 (95.0%)	226 (94.2%)	664 (92.7%)
Discontinued Treatment Prematurely	31 (13.0%)	10 (4.2%)	11 (4.6%)	52 (7.3%)
Discontinued Study prematurely	21 (8.8%)	6 (2.5%)	6 (2.5%)	33 (4.6%)
Safety Evaluable Population received study medication, as treated	236 (99.2%)	238 (100%)	239 (99.6%)	713 (99.6%)
Intent-to-treat Population ≥ 1 on therapy study visit	236 (99.2%)	238 (100%)	239 (99.6%)	713 (99.6%)
Per Protocol Population (for the analysis of 4 m BCVA at Month 12) No on-therapy study visits or protocol violation	176 (73.9%)	200 (84.0%)	196 (81.7%)	572 (79.9%)
Excluded from PP Population	62 (26.1%)	38 (11.8%)	44 (18.3%)	144 (20.1%)
Pharmacokinetic-Evaluable Population	218 (91.6%)	226 (95.0%)	225 (93.8%)	669 (93.4%)

a Defined as having a visual acuity score in the study eye at Month 12. Data from subjects who missed the Month 12 visit but stayed in the study for the second year were not counted.

Reviewer's Comments:

Overall, the study had good retention of subjects through Month 12. The sham injection group had significantly more discontinuations than either ranibizumab treatment group.

Two subjects in the sham group and one subject in the ranibizumab 0.5mg group did not receive any study treatment.

Table 6.1.3.1-6 Major Protocol Deviations during the First Treatment Year Randomized Subjects

Deviation	Sham (N=238)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=240)
Any deviation	55 (23.1%)	57 (23.9%)	62 (25.8%)
Re-randomized	0	0	1 (0.4%)
Dosing error: Overdose	0	1 (0.4%)	1 (0.4%)
Dosing Error: Procedure (injection) accident	0	1 (0.4%)	1 (0.4%)
Dosing Error: Sham injection performed	0	2 (0.8%)	1 (0.4%)
Treatment assignment unmasked [a]	1 (0.4%)	0	4 (1.7%)
Ineligible per protocol off-label PDT use	9 (3.8%)	0	0
Received PDT <21 days after a study drug injection			
Study eye	1 (0.4%)	0	0
Fellow eye	4 (1.7%)	9 (3.8%)	2 (0.8%)
Pre-treatment procedure not followed	5 (2.1%)	1 (0.4%)	4 (1.7%)
Dose-holding criteria not followed	1 (0.4%)	4 (1.7%)	1 (0.4%)
Visual acuity (4 m) not assessed at baseline: study eye	9 (3.8%)	9 (3.8%)	10 (4.2%)
Visual acuity (2 m) assessment incomplete: letters smaller than 20/20 not adequately tested			
Study eye	0	2 (0.8%)	3 (1.3%)
Fellow eye	24 (10.1%)	10 (4.2%)	13 (5.4%)
ETDRS chart with notation for 2-m testing was used	1 (0.4%)	3 (1.3%)	2(0.8%)
ETDRS charts switch usage (left eye chart vs. right eye chart)	0	0	1 (0.4%)
Slit lamp was performed after injection			
On Day 0	1 (0.4%)	2 (0.8%)	1 (0.4%)
At any visit other than Day 0	1 (0.4%)	2 (0.8%)	1 (0.4%)
Required a reader/translator's help for VFQ-25 and other questionnaires	1 (0.4%)	0	1 (0.4%)
Vital signs assessed pre-dose	7 (2.9%)	6 (2.5%)	9 (3.8%)
Inconsistent method for IOP measurement	11 (4.6%)	20 (8.4%)	22 (9.2%)

a Only study coordinators were unmasked for one case in the sham-injection group and two cases in the 0.5 mg group.

Reviewer's Comments:

There were slightly more protocol deviations in the ranibizumab 0.5 mg group.

The protocol deviations which occurred most frequently were an inconsistent method for IOP measurement, incomplete assessment of 2 m visual acuity in the fellow eye, and failure to assess 4m visual acuity at baseline.

Table 6.1.3.1-7 Discontinued Subjects and Reason
Study FVF2598g

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
		Study Group	
S07438	101015	Subject's Decision	332
S08127	102010	AE - Worsening AMD	127
S08536	102014	AE - Pneumonia, COPD Exacerbation x 2	265
S08255	103006	AE - Worsening AMD	148
S08215	104010	Subject's Decision – no improvement in VA	284
S08165	106006	Physician's Decision – IntraVit Kenalog given	236
S07439	112005	Randomized in error	93
S08082	119005	Lost to follow-up	36
S08239	121004	Subject's Decision / AE – Mild iritis	158
S08235	124001	Subject's Decision – Never received treatment	1
S08130	125008	AE - 30 letter loss of vision – Worsened AMD	50
S08246	131011	Subject's Decision	239
S08111	133001	Subject's Condition Mandated Other Treatment	154
S08248	140001	AE – Lung lesion, elevated liver enzymes	259
S08586	141017	Randomized in error	1
S08088	142002	Subject's Decision	127
S08212	144002	AE - Worsening AMD	127
S08212	144005	Lost to follow-up	331
S08187	149003	Subject's Decision	36
S08187	149007	AE - Worsening AMD	359
S08187	149009	Subject's Decision	127
S00399	162003	Subject's Decision	8
S08133	164002	Subject's Decision	120
S08231	166001	AE - Worsening AMD	295
S00266	167008	Subject's Condition Mandated Other Treatment	309
S08146	175002	AE – Lung cancer treatment	176
S08194	176005	Subject's Decision	317
S02507	186002	Subject's Condition Mandated Other Treatment	162
S07387	187002	AE – Acute Gout	359
S08252	193004	AE - Worsening AMD	133
S08882	205002	AE - Death due to Asthma / COPD	333
		0.3 mg Group	
S07438	101020	AE - Death – Myocardial infarction	12
S08127	102006	AE – Lymphoma	372
S08536	102015	Subject's Decision	258
S08144	110002	Subject's Decision	324
S08092	111005	AE – Severe aortic stenosis	96
S08190	120005	AE - Worsening AMD	66
S08246	131003	AE – Vulvar adenocarcinoma	210
S08189	160001	AE – Iritis	121
S00399	162002	AE – Loss of vision	100
S08084	196004	Lost to follow-up	218
		0.5 mg Group	
S08092	111003	AE – Cardiac arrhythmia	100
S08082	119004	Subject's Decision	1
S07442	127002	Subject's Decision – Did not receive treatment	28

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Study Site ID	Subject ID	[illegible]	Study Day
S08081	130013	AE – Fractured pelvis	39
S08246	131001	AE – Stroke	244
S08246	131007	AE – Death due to small bowel infarct	178
S08238	138002	AE – Recurrent iritis	153
S08231	166002	Worsening AMD	241
S07479	173002	Non-compliance	28
S08232	181004	AE – Death – Asthma	155
S08084	196003	AE – Cough and wheezing	92

Reviewer's Comment:
The majority of subjects who discontinued treatment were in the sham-injection group. The most frequent reasons for discontinuation were worsening AMD, worsening vision, or subject's decision with no improvement in vision.

In the ranibizumab groups, adverse events related to systemic disease were the most frequent causes of treatment discontinuation. There was no pattern of non-ocular adverse event which led to discontinuation.

Table 6.1.3.1-8 Demographic Statistics by Treatment Group
Intent-to-Treat, Randomized Subjects

Demographic	Sham (n = 238)	Ranibizumab 0.3 mg (n = 238)	0.5 mg (n = 240)
Age (yr)			
Mean (SD)	77.0 (6.6)	77.4 (7.6)	76.8 (7.6)
Range	56–94	52–95	52–93
Age group (yr)			
50 to < 65	11 (4.6%)	13 (5.5%)	16 (6.7%)
65 to < 75	67 (28.2%)	64 (26.9%)	64 (26.7%)
75 to < 85	132 (55.5%)	130 (54.6%)	124 (51.7%)
≥ 85	28 (11.8%)	31 (13.0%)	36 (15.0%)
Sex			
Male	79 (33.2%)	85 (35.7%)	88 (36.7%)
Female	159 (66.8%)	153 (64.3%)	152 (63.3%)
Race/ethnicity			
White	231 (97.1%)	229 (96.2%)	232 (96.7%)
Asian or Pacific Islander	2 (0.8%)	3 (1.3%)	2 (0.8%)
Hispanic	5 (2.1%)	5 (2.1%)	6 (2.5%)
Other	0	1 (0.4%)	0

Reviewer's Comment:
The demographics of the treatment groups were balanced. The majority of the patients randomized and treated in this study were elderly and white.

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Table 6.1.3.1-9 Baseline Ocular Characteristics in the Study Eye Intent-to-Treat, Randomized Subjects

Characteristics	Sham (n = 238)	Ranibizumab 0.3 mg (n = 238)	Ranibizumab 0.5 mg (n = 240)
Years since first diagnosis of neovascular AMD			
N	235	238	238
Mean (SD)	0.8 (1.3)	0.6 (1.6)	0.7 (1.3)
Range	0.0 – 10.9	0.0 – 18.9	0.0 - 13.3
Visual acuity at a starting test distance of 4 meters			
N	229	229	230
Number of letters (0–100)			
Mean (SD)	53.5 (14.7)	53.2 (13.6)	53.2 (14.9)
Range	0–88	0–82	0–80
≤ 54	111 (48.5%)	114 (49.8%)	110 (47.8%)
≥ 55	118 (51.5%)	115 (50.2%)	120 (52.2%)
Approximate Snellen equivalent			
Median	20/80	20/80	20/80
20/200 or worse	26 (11.4%)	28 (12.2%)	36 (15.7%)
Better than 20/200 but worse than 20/40	171 (74.7%)	172 (75.1%)	159 (69.1%)
20/40 or better	32 (14.0%)	29 (12.7%)	35 (15.2%)
Intraocular pressure (mmHg)			
N	238	238	240
Mean (SD)	14.8 (3.2)	14.8 (3.1)	14.8 (3.2)
Range	7–24	5–25	8–25
0–21	234 (98.3%)	233 (97.9%)	236 (98.3%)
22–29	4 (1.7%)	5 (2.1%)	4 (1.7%)

Reviewer's Comment:

There was no significant difference in baseline vision or intraocular pressure characteristics between the treatment groups.

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Table 6.1.3.1-10 Fluorescein Angiography and Fundus Photography Characteristics of the Study Eye at Baseline Intent-to-Treat, Randomized Subjects

Characteristics	Sham (n = 238)	Ranibizumab 0.3 mg (n = 238)	Ranibizumab 0.5 mg (n = 240)
CNV classification			
Predominantly classic	0	1 (0.4%) [a]	1 (0.4%) [b]
Minimally classic	87 (36.6%)	86 (36.1%)	91 (37.9%)
Occult without classic	151 (63.4%)	151 (63.4%)	148 (61.7%)
Total area of lesion (DA)			
Mean (SD)	4.41 (2.48)	4.26 (2.54)	4.47 (2.62)
Range	0.20–11.75	0.10–11.80	0.25–12.00
≤ 4 DA	124 (52.1%)	134 (56.3%)	125 (52.1%)
> 4 DA	114 (47.9%)	104 (43.7%)	115 (47.9%)
Total area of CNV (DA)			
Mean (SD)	4.28 (2.41)	4.13 (2.47)	4.27 (2.51)
Range	0.20–11.75	0.02–11.80	0.12–12.00
Area of classic CNV (DA)			
Mean (SD)	0.17 (0.36)	0.16 (0.35)	0.17 (0.38)
Range	0.00–2.50	0.00–2.50	0.00–2.25
Total area of leakage from CNV plus intense progressive RPE staining (DA) [c]			
Mean (SD)	3.54 (2.47)	3.59 (2.50)	3.47 (2.63)
Range	0.00–12.85	0.00–11.95	0.00–13.50
Area of serous sensory retinal detachment or subretinal fluid (DA)			
Mean (SD)	4.45 (3.44)	4.52 (3.54)	4.50 (3.48)
Range	0.00–16.00	0.00–17.00	0.00–16.00
Occult CNV present	238 (100%)	235 (98.7%)	237 (98.8%)

a The subject was enrolled as a result of the site misinterpreting the lesion eligibility confirmation from the reading center.

b Re-categorization as predominantly classic CNV by the reading center post-randomization.

c n=220 for the sham-injection group, and n=218 for each ranibizumab group l

Reviewer's Comment:

There was no significant difference in the baseline characteristics of the CNV lesions across the treatment groups.

Approximately two- thirds of the subjects had occult lesions without any classic component in each treatment group.

Table 6.1.3.1-11 Concurrent Ocular Procedures and Select Concomitant Medications during the First Treatment Year: Randomized Subjects

Procedure or Medication	[redacted]	Ranibizumab 0.3 mg (n =238)	Ranibizumab 0.5 mg (n = 240)
Concurrent ocular procedures, study eye [a, b]			
PDT	25 (10.5%)	1 (0.4%)	0
Any procedure other than PDT	10 (4.2%)	14 (5.9%)	12 (5.0%)
AMD-related	8 (3.4%)	0	3 (1.3%)
Cataract	1 (0.4%)	4 (1.7%)	2 (0.8%)
Glaucoma	0	0	1 (0.4%)
Vitreoretinal disease	0	2 (0.8%)	2 (0.8%)
Other disease	1 (0.4%)	7 (2.9%)	5 (2.1%)
Concomitant ocular medications, study eye [c]			
Any medication use	183 (76.9%)	194 (81.5%)	199 (82.9%)
IOP lowering agents	23 (9.7%)	34 (14.3%)	33 (13.8%)
β-adrenoceptor blocking agents	13 (5.5%)	18 (7.6%)	17 (7.1%)
Dermatologic agents	12 (5.0%)	16 (6.7%)	19 (7.9%)
Fluoroquinolones	11 (4.6%)	12 (5.0%)	15 (6.3%)
Mild analgesics	6 (2.5%)	13 (5.5%)	15 (6.3%)
Ophthalmic preparations	36 (15.1%)	38 (16.0%)	40 (16.7%)
Pharmaceutical aids	10 (4.2%)	18 (7.6%)	17 (7.1%)
Steroids	14 (5.9%)	11 (4.6%)	16 (6.7%)
Vitamins and minerals	123 (51.7%)	145 (60.9%)	141 (58.8%)
Concomitant Non-Ocular Medications [d]			
Any medication use	236 (99.2%)	238 (100%)	238 (99.2%)
Antacids	30 (12.6%)	20 (8.4%)	20 (8.3%)
Antianemic agents	35 (14.7%)	23 (9.7%)	31 (12.9%)
Antianxiety agents	18 (7.6%)	37 (15.5%)	35 (14.6%)
Antidepressants	36 (15.1%)	43 (18.1%)	53 (22.1%)
Antihypertensive agents	38 (16.0%)	53 (22.3%)	62 (25.8%)
Antirheumatic and anti-inflammatory agents	84 (35.3%)	69 (29.0%)	80 (33.3%)
β-adrenoceptor blocking agents	71 (29.8%)	81 (34.0%)	76 (31.7%)
Bronchodilators and anti-asthmatics	20 (8.4%)	30 (12.6%)	30 (12.5%)
Calcium regulators and replenishers	80 (33.6%)	87 (36.6%)	81 (33.8%)
Diuretics	73 (30.7%)	82 (34.5%)	76 (31.7%)
Expectorants	18 (7.6%)	16 (6.7%)	8 (3.3%)
Histamine H2-receptor antagonists	29 (12.2%)	17 (7.1%)	28 (11.7%)
Hypolipidemics	104 (43.7%)	114 (47.9%)	109 (45.4%)
Mild analgesics	147 (61.8%)	143 (60.1%)	153 (63.8%)
Penicillins	13 (5.5%)	27 (11.3%)	21 (8.8%)
Steroids	60 (25.2%)	65 (27.3%)	50 (20.8%)
Supplements	45 (18.9%)	47 (19.7%)	35 (14.6%)
Vitamins and minerals	144 (60.5%)	138 (58.0%)	127 (52.9%)

a Based on data recorded on the Verteporfin PDT CRF pages.

b Based on the procedures reported on the Concurrent Ocular Procedure CRF pages, which were designed to capture all procedures other than PDT.

c Tabulation was based on medication use reported on the Concomitant Medications CRF pages for medications used by ≥ 5% of subjects in any group.

d Tabulation was based on medications reported on the Concomitant Medications CRF pages. Only the medications satisfying any of the following criteria were presented: used by ≥ 25% of subjects in any group at

screening, used by ≥ 30% of subjects in any group during Year 1, or with a >4% difference between sham and either ranibizumab group.

Reviewer's Comment:

In the ranibizumab 0.5 mg group, the procedures other than PDT performed were usually related to cataract surgery.

Table 6.1.3.1-12 Prior Therapies for AMD in the Study Eye Randomized Subjects

	Sham (n=238)	Ranibizumab 0.3 mg (n=238)	Ranibizumab 0.5 mg (n=240)
Any prior therapy for AMD	134 (56.3%)	140 (58.8%)	137 (57.1%)
Laser photocoagulation	22 (9.2%)	13 (5.5%)	14 (5.8%)
Medication	4 (1.7%)	3 (1.3%)	3 (1.3%)
Supplements	119 (50.0%)	132 (55.5%)	125 (52.1%)
Other	8 (3.4%)	3 (1.3%)	2 (0.8%)

Reviewer's Comment:

The treatment groups were well balanced with regard to prior treatment for age-related macular degeneration. Almost twice as many patients had prior laser photocoagulation in the sham group than in the ranibizumab groups.

Table 6.1.3.1-13 Concurrent PDT and Intravitreal Steroid Treatment in the Study Eye – Randomized Subjects

	Sham (n=238)	Ranibizumab 0.3 mg (n=238)	Ranibizumab 0.5 mg (n=240)
Concurrent PDT	25 (10.5%)	1 (0.4%)	0
Intravitreal steroid injection	6 (2.5%)	0	0

Reviewer's Comment:

The vast majority of on-study PDT treatments and all intravitreal steroid injections were received by those in the sham injection group.

6.1.3.2 Study FVF2587g

Title: A Phase 3, Multicenter, Randomized, Double-Masked, Active Treatment-Controlled Study of the Efficacy and Safety of rhuFab V2 (Ranibizumab) Compared with Verteporfin (Visudyne) Photodynamic Therapy in Subjects With Predominantly Classic Subfoveal Neovascular Age-Related Macular Degeneration.

Objectives: Primary:

- To evaluate the efficacy of intravitreal injections of ranibizumab administered monthly compared with verteporfin photodynamic therapy (PDT) 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.
    - The non-inferiority of ranibizumab to verteporfin PDT was evaluated; if non-inferiority was demonstrated, then the treatment differences between ranibizumab and verteporfin PDT were also to be evaluated for superiority.
- To evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly.

Secondary:

- To evaluate the efficacy of monthly intravitreal injections of ranibizumab in preventing vision loss as measured by the following:
    - Mean change from baseline in visual acuity over time up to 12 months
    - Proportion of subjects who gained at least 15 letters in visual acuity at 12 months compared with baseline
    - Proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 12 months
- To investigate the efficacy of monthly intravitreal injections of ranibizumab on vision-related functioning and well-being assessed during a period of 12 months, as measured by the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25)
- To evaluate the efficacy of monthly intravitreal injections of ranibizumab on the size of classic choroidal neovascularization (CNV) and amount of leakage from CNV at 12 months, as assessed by fluorescein angiography

Study Design: Phase 3, multicenter (100 sites), randomized, double-masked, active treatment-controlled study of intravitreally administered ranibizumab compared with verteporfin PDT. Approximately 426 subjects with primary or recurrent subfoveal CNV secondary to AMD who had predominantly classic lesions were to be enrolled.

Test Drug Schedule:

Eligible subjects were randomized in a 1:1:1 ratio to receive one of the following:

- 0.3 mg ranibizumab and sham PDT with saline infusion,
- 0.5 mg ranibizumab and sham PDT with saline infusion, or
- Sham injection of ranibizumab and active verteporfin PDT.

Verteporfin/sham PDT was administered prior to the ranibizumab/sham injection to ensure the best practice with respect to aseptic technique and to attempt to minimize the risk of infection. Subjects received a ranibizumab or sham injection monthly (30 ± 7 days) for 23 months of treatment (24 injections) and active (verteporfin) or sham (saline) PDT on Day 0 and every 3 months if needed (as determined by the assessment of fluorescein angiograms by the evaluating physician) for 21 months of treatment.

Table 6.1.3.2-1 Clinical Sites - Study FVF2587g

Site Number	Investigator Name Location Investigator Number	Verteporfin PDT N=143	Ranibizumab		All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	

4 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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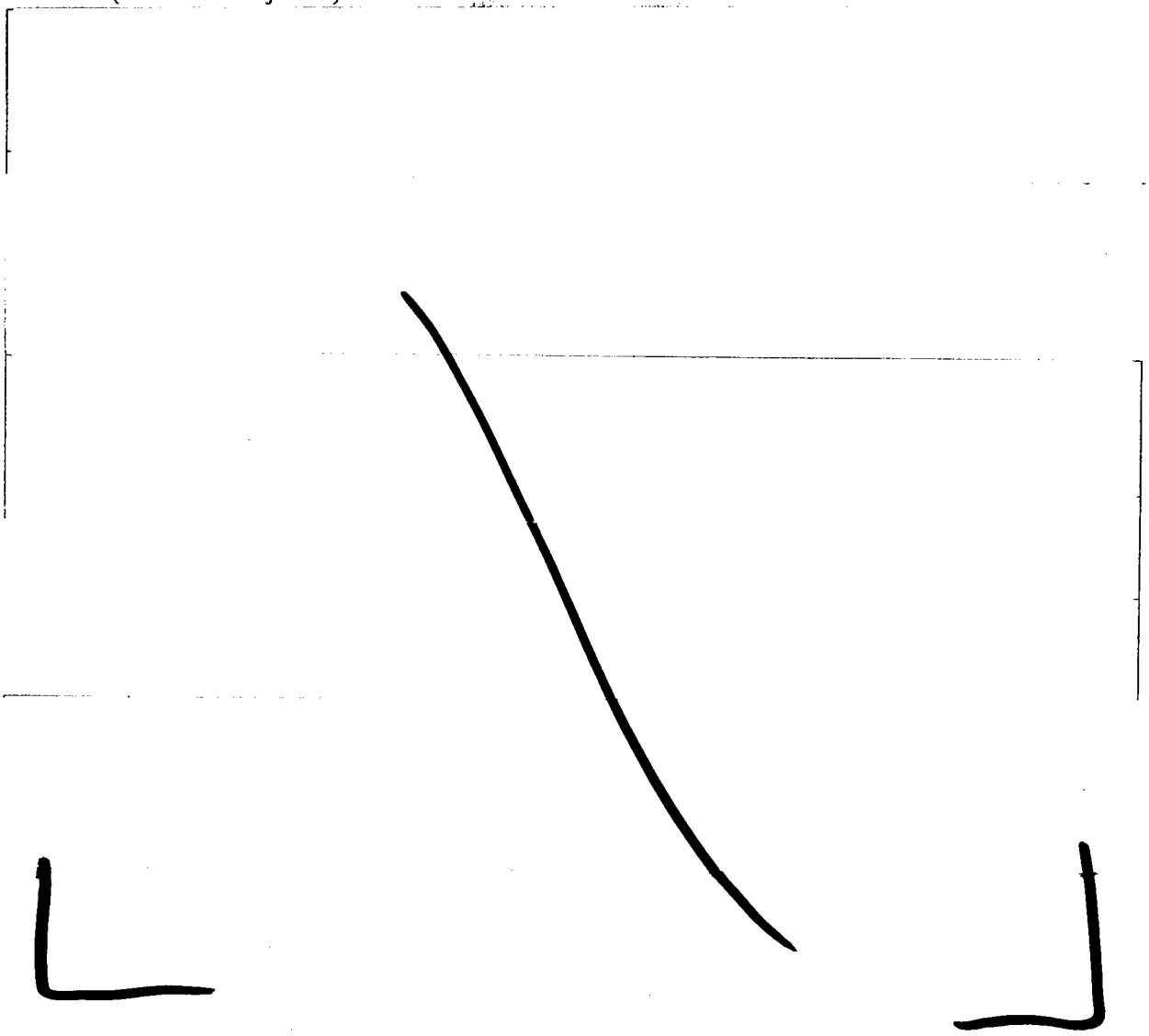

Overall Study Design

This was a Phase 3, multicenter, randomized, double-masked, active treatment controlled study of intravitreally administered ranibizumab compared with verteporfin PDT. Approximately 426 subjects with primary or recurrent subfoveal CNV secondary to AMD who had predominantly classic lesions were to be enrolled. The study was to be conducted at approximately 100 study sites. The study design was essentially the same as Study 98.

Fluorescein angiograms were sent to a central reading center to determine CNV classification for study eligibility. Eligible subjects were randomized in a 1:1:1 ratio to receive one of the following treatments:

- 0.3 mg ranibizumab and sham PDT with saline infusion,
- 0.5 mg ranibizumab and sham PDT with saline infusion, or
- Sham injection of ranibizumab and active verteporfin PDT.

Randomization was stratified by the visual acuity score at Day 0 (≤44 letters [approximately worse than 20/125] vs. ≥45 letters [approximately 20/125 or better] based on the ETDRS chart and assessment at a starting distance of 2 meters) and by study center. Verteporfin/sham PDT was administered prior to the ranibizumab/sham injection. Subjects received a ranibizumab or sham injection monthly (30 ± 7 days) for 23 months of treatment (24 injections) and active (verteporfin) or sham (saline) PDT on Day 0 and every 3 months if needed (as determined by the assessment of fluorescein angiograms by the evaluating physician) for 21 months of treatment. To preserve masking, administration of sham PDT with saline infusion mimicked that of active verteporfin PDT, and administration of active verteporfin PDT was in accordance with the Visudyne prescribing information.

There was a minimum of two investigators per study site to fulfill the masking requirements of this study. At least one investigator was designated as the evaluating physician, who was masked to the treatment assignment and conducted all ocular assessments. At least one other investigator was designated as the injecting physician, who was unmasked to the treatment assignment and performed the ranibizumab or sham injection procedures and the active or sham PDT infusion procedures, but who was masked to the ranibizumab dose (0.3 mg or 0.5 mg).

Study Population

Inclusion/Exclusion Criteria

Essentially the same as Study 98 except that patients had predominately classic choroidal neovascularization.

Outcome Measures

Essentially the same as Study 98 except that patients had predominately classic choroidal neovascularization.

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint.

Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters, not 2 meters.

Study Treatments

Dosing and Administration of Ranibizumab and Sham

Ranibizumab was administered intravitreally in a multiple-dose regimen of either 0.3 mg or 0.5mg of ranibizumab every month (Day 0-Month 23) for a total of 24 injections. Sham intravitreal injections were administered according to the same dosing schedule as ranibizumab injections: every month (Day 0 – Month 23) for a total of 24 injections. Dosing was not to occur earlier than 14 days after the previous treatment. Missed doses were not to be replaced.

Verteporfin/sham PDT was to be administered prior to the ranibizumab/sham injection to ensure the best practice with respect to aseptic technique and to attempt to minimize the risk of injection. The injecting physician(s) (and any assistants, if applicable) performing the ranibizumab/sham injections could not be involved in any other aspect of the study in any way, and could not divulge the treatment assignment to anyone. The evaluating physician(s) was responsible for all other aspects of the study except for the intravitreal injection procedure, intravenous administration of verteporfin or saline, and 689-nm (± 3 nm) diode laser irradiation of the macula. Visits for injection days had to be scheduled when both physicians were present. The subjects, all site personnel (except for the injecting physician(s) and designated site personnel needed to assist with the injection procedure), and all Sponsor personnel (with the exception of drug accountability monitors, corporate compliance staff, and finance) were masked to treatment assignment.

Dosing and Administration of Verteporfin PDT

Verteporfin PDT was to be administered every 3 months (if needed) as determined by the evaluating physician's assessment of fluorescein angiography. The injecting physician determined the spot diameter of the area to be treated. Active verteporfin PDT or sham PDT with saline infusion was only to be administered on Day 0 and, if needed, at Months 3, 6, 9, 12, 15, 18 and 21.

Dosing and Administration of Sham PDT with Saline Infusion

The sham PDT with saline infusion mimicked active verteporfin PDT and was administered in accordance with Visudyne prescribing information. On Day 0, all subjects received either active or sham PDT followed by an injection of ranibizumab or a sham injection, respectively. The injecting physician and assistant and/or pharmacist were aware of the treatment assignment. If a subject received an injection of ranibizuamab, he or she received sham PDT (saline infusion followed by 689-nm [±3 nm] diode laser light dose and intensity was to be the same as those used for verteporfin PDT (i.e., light dose of 50J/cm2 at an intensity of 600 mW/cm2 administered over 83 seconds). If a subject received a sham injection, he or she received active PDT (verteporfin infusion followed by 689-nm [±3 nm] diode laser irradiation to the macula). Following Day 0, the evaluating physician determined the need for PDT every 3 months (i.e., 3, 6, 9, 12, 115, 18 and 21) based on his or her assessment of ophthalmoscopic findings and fluorescein angiography results.

Table 6.1.3.2-3 Study Treatment Holding Criteria

Event	Action to be Taken
Intraocular inflammation	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if intraocular inflammation is ≥ 2+ in the study eye.
Visual acuity loss	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if there is a treatment-related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of visual acuity prior to the most recent treatment.
Intraocular pressure	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if IOP in the study eye was ≥ 30 mmHg. Treatment will be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the evaluating physician.
Vitreous hemorrhage	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if there is a ≥ 2+ vitreous hemorrhage and ≥ 30-letter decrease in visual acuity in the study eye compared with the last assessment of visual acuity prior to the onset of the vitreous hemorrhage. Treatment will be permitted when the vitreous hemorrhage improves to <2+ or visual acuity score improved to a <30-letter decrease.
Sensory rhegmatogenous retinal break or detachment (including macular hole)	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if a retinal break was present in the study eye. Treatment may be resumed ≥ 28 days after the retinal break has been successfully treated. Subjects with a rhegmatogenous retinal detachment or Stage 3 or 4 macular hole were discontinued from treatment for the duration of the study.
Subfoveal hemorrhage	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if there is a subretinal hemorrhage involving the center of the fovea in the study eye, if the size of the hemorrhage was either ≥ 50% of the total lesion area or ≥ 2 DAs in size.
Local or systemic infection	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if any of the following were present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye, or if the subject was receiving treatment for a severe systemic infection.
Intraocular surgery	Hold active/sham PDT **and** ranibizumab/sham intravitreal injection if intraocular surgery had been performed in the study eye within the previous 28 days.

In this study, no subject was to receive both active verteporfin PDT and active ranibizumab injection in the study eye. If unmasked personnel discovered that a subject randomized to receive active ranibizumab injection received active verteporfin PDT in the study eye in error, then the active ranibizumab injection for the current month was to be held and the next ranibizumab injection for the subject was to be administered no earlier than 28 days after the day on which the active verteporfin PDT was received.

Additionally, the evaluating physician could discontinue a subject from treatment for other safety reasons. If a subject missed more than two ranibizumab/sham injections in a treatment year, serious consideration was to be given by the evaluating physician and the Sponsor to withdrawing the subject from the study.

Efficacy Analyses

The primary, secondary, and most of the exploratory efficacy endpoints were analyzed for randomized subjects based on the treatment assigned at randomization. Missing data were imputed using the last-observation-carried forward (LOCF) approach.

Comparisons of efficacy were performed between each ranibizumab dose group and the verteporfin PDT (control) group. All pairwise comparisons for assessing treatment difference were performed using a statistical method that includes only two treatment groups (ranibizumab vs. control) at a time. For the primary efficacy endpoint, an adjustment was made for multiple treatment comparisons of each ranibizumab dose group with the control group. For secondary efficacy endpoints, adjustments for multiplicity of endpoints were also made to manage the Type I error rate.

Primary Efficacy Endpoint. The primary efficacy endpoint was the proportion of subjects who lost fewer than 15 letters in BCVA score at Month 12 compared with baseline, based on assessment at a starting test distance of 2 meters. The primary efficacy endpoint was analyzed for randomized subjects based on the treatment assigned at randomization, with missing data imputed using the LOCF method. Supportive sensitivity analyses were performed as well.

For each ranibizumab dose group, non-inferiority to the control group was tested using a one-sided testing procedure (or equivalently, using a one-sided CI) and a non-inferiority limit. Subject to the procedures for controlling overall Type I error, a test for a treatment difference compared with the control group could also be performed for each dose group.

To adjust for multiple comparisons of two ranibizumab dose groups with the control group, a Hochberg-Bonferroni multiple comparison procedure was used (Hochberg 1988).

The non-inferiority limit was based on the results of the Phase 3 trials of verteporfin PDT versus placebofrom the TAP Study. The value of 0.07 is approximately one-half of the minimum estimated difference (lower limit of a two-sided 95% CI) in the proportion of subjects with predominantly classic CNV who lost fewer than 15 letters at Month 12. For subjects with predominantly classic CNV, these proportions were 0.673 for verteporfin PDT–treated subjectsand 0.393 for placebo-treated subjects, for an estimated treatment effect of 0.28 (95% CI, 0.153 to 0.407, using the normal approximation to the binomial distribution). It is also the case that 0.07 is equal to 25% of the treatment effect of verteporfin PDT versus placebo.

Laboratory Tests. Descriptive summaries of laboratory values, including changes from baseline and treatment-emergent abnormalities, were generated. The number and percentage of subjects with serum antibodies to ranibizumab at baseline and during the treatment period were tabulated.

Vital Signs and Physical Findings. Descriptive summaries of vital sign measurements and changes from baseline were generated.

Ocular Assessments. Results of the following ocular assessments were summarized by timepoint and by eye (study vs. fellow) using descriptive summaries: visual acuity, intraocular pressure, slitlamp examination, indirect ophthalmoscopy, fluorescein angiography, and fundus photography. The changes from baseline in intraocular pressure were tabulated. The presence of intraocular inflammation and vitreous hemorrhage, as determined from the slit lamp examination, were tabulated by grade (according to grading scales for flare/cells and vitreous

hemorrhage density). The presence of retinal break or detachment as determined from indirect ophthalmoscopy was tabulated.

Determination of Sample Size

The sample size was determined based on the analysis of the primary efficacy endpoint for treatment differences between each ranibizumab dose group and the control group. The planned sample size of 426 subjects was based on calculations using the following assumptions: 1:1:1 randomization ratio (0.3 mg of ranibizumab vs. 0.5 mg of ranibizumab vs. verteporfin PDT), the Pearson $\chi 2$ test for comparison of two proportions (for each ranibizumab group vs. verteporfin PDT), and the Hochberg-Bonferroni multiple comparison procedure at an overall Type I error rate of 0.0497 (after adjustment for three planned interim safety analyses prior to the analysis of the primary efficacy endpoint). The power of the Hochberg-Bonferroni multiple comparison procedure was evaluated using Monte Carlo simulations.

The sample size of 426 subjects with predominantly classic CNV provided 96% power in the primary ITT analysis based on randomized subjects to detect a statistically significant difference between one or both ranibizumab groups and the verteporfin PDT group in the percentage of subjects who lost fewer than 15 letters in visual acuity score at Month 12, assuming a rate of 84% in each ranibizumab group and 67% in the verteporfin PDT group.

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Table 6.1.3.2-4
Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

Study Period	Screen	Treatment Phase														Early Termination
		Day		Month												
	-28 to -1	0	7	1	2	3	4	5	6	7	8	9	10	11	12	
Assessment Window (Days)	–	–	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±30
Informed Consent	x															
Inclusion/Exclusion Criteria	x															
Demographic data	x															
Height and Weight	x															
Medical and surgical history [b]	x															
VFQ-25 [c]		x		x	x	x			x			x			x	x
SF-36 Health Survey [c]		x							x						x	x
HUI (at selected sites only) [c]	x					x				x			x			x
VAS [c]	x			x	x	x				x			x			x
Review of Body Systems	x														x	x
Serum pregnancy test [d]	x															
Contrast Sensitivity test [e, f]	x		x	x	x	x			x						x	x
Best corrected visual acuity (2 meter starting distance) [e, f]	x	x [g]	x	x	x	x	x	x	x	x	x	x	x	x	x [g]	x [g]

a For subjects who withdrew from the study early. Performed 30 days (±7 days) following the last injection or study visit.
b Significant medical/surgical history, including chronic and ongoing conditions (e.g., trauma, cancer history, and ophthalmic history).
c VFQ-25 (where local languages were available), SF-36 Health Survey (where local languages are available), HUI questionnaire (selected sited only), and VAS were to be administered to the subject prior to the subject's completing any other study procedures.
d For women of childbearing potential.
e Performed pre-treatment
f Performed prior to dilating eyes
g Also assessed at a starting test distance of 4 meters after assessing at a starting test distance of 2 meters

Study Period	Screen	Treatment Phase														Early Term.[a]
		Day		Month												
	-28 to -1	0	7	1	2	3	4	5	6	7	8	9	10	11	12	
Assessment Window (Days)	–	–	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	30±7
Slit Lamp Examination [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect and high-magnification ophthalmoscopy [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lens status assessment		x													x	
Fundus Photography [e]	x					x [h]			x [h]			x [h]			x [h]	x
Fluorescein Angiography [e]	x					x [h]			x [h]			x [h]			x [h]	x
OCT (at selected sites) [e]		x	x	x											x	x
Laboratory Samples [e, i]	x														x	x
Serum samples for antibodies to ranibizumab and pharmacokinetic sample [e]	x								x						x	x
Intraocular pressure [j, k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Active (verteporfin) or sham (saline) photodynamic therapy (study eye only) [l]		x				x [m]			x [m]			x [m]			x [m]	
Ranibizumab administration or sham injection (study eye only)		x		x	x	x	x	x	x	x	x	x	x	x	x	
Finger count, hand motion, light perception n		x		x	x	x	x	x	x	x	x	x	x	x	x	
Vital Signs [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x

h Fluorescein angiography and color fundus photography were to be performed within 7 days prior to the scheduled study visit to allow adequate time for the evaluating physician to determine if PDT was necessary.
i Laboratory evaluations included hematology, blood chemistry, and urinalysis.
j The measurement method used for a subject was to remain consistent throughout the study.
k Obtained pre-treatment for both eyes and 60 minutes (±10 minutes) post-injection for study eye only.
l Active (verteporfin) or sham (saline) PDT, if needed or required by the protocol (Day 0), were to be administered prior to ranibizumab/sham injection (all timepoints).
m Active (verteporfin) or sham (saline) PDT was administered based on need, as determined by assessment of fluorescein angiograms by the evaluating physician (Months 3, 6, 9 and 12 only).
n Injecting physician was to be performed within 15 minutes post-injection for study eye only.
o Performed post-treatment

Study Period	Screen	Treatment Phase														Early Term.[a]
	Day			Month												
	-28 to -1	0	7	1	2	3	4	5	6	7	8	9	10	11	12	
Assessment Window (Days)	--	--	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	30±7
Concomitant Medications [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events [e, o, q]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact [r]		x		x	x	x	x	x	x	x	x	x	x	x	x	

p Recorded any prescription drugs or over-the-counter preparations other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes, etc.) and pre- and post-injection medications used by a subject within 7 days preceding Day0.

q Adverse events were to be collected from Day 0 through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab were to be followed, even after the subject's study anticipation was over, until the event resolved or the event was assessed as irreversible, chronic or stable.

r Subjects were contacted 2 days (±1 day) following treatment to elicit reports of any decreased in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they had taken the prescribed post-injection antimicrobials.

Table 6.1.3.2-4
Study Flowchart: Screening, Treatment Phase Day 0 through Month 12, and Early Termination

Study Period	Treatment Phase												Early Term.[a]
	Month												
	13	14	15	16	17	18	19	20	21	22	23	24	
Assessment Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	30±7
VFQ-25 [b]	X	X	X			X			X			X	X
SF-36 Health Survey [b]						X						X	X
HUI (at selected sites only) [b]			X				X			X			X
VAS [b]	X	X	X				X			X			X
Review of Body Systems												X	
Best corrected visual acuity (2 meter starting distance) [c, d]	X	X	X	X	X	X	X	X	X	X	X	X [e]	X [c]
Slit Lamp Examination [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated binocular indirect and high-magnification ophthalmoscopy [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Lens status assessment												X	
Fundus Photography			X [f]			X [f]			X [f]			X	X
Fluorescein Angiography			X [f]			X [f]			X [f]			X	X

a For subjects who withdrew from the study early. Performed 30 days (±7 days) following the last injection or study visit.
b VFQ-25 (where local languages were available), SF-36 Health Survey (where local languages are available), HUI questionnaire (selected sited only), and VAS were to be administered to the subject prior to the subject's completing any other study procedures.
c Performed pre-treatment
d Performed prior to dilating eyes.
e Also assess at a starting distance of 4 meters after assessing at a starting test distance of 2 meters.
f Fluorescein angiography and color fundus photography may have been performed within 7 days prior to the scheduled study visit to allow adequate time for the evaluating physician to determine if PDT is necessary.

Study Period	Treatment Phase												Early Term[a]
	Month												
	13	14	15	16	17	18	19	20	21	22	23	24	
Assessment Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	30±7
Contrast Sensitivity [d]												x	x
Laboratory Samples [g]												x	x
Serum antibodies to ranibizumab and serum pharmacokinetic sample [e]												x	x
Intraocular pressure [h, i]	x	x	x	x	x	x	x	x	x	x	x	x	x
Active (verteporfin) or sham (saline) photodynamic therapy (study eye only) [j]			x [k]			x [k]			x [k]				
Ranibizumab administration or sham injection (study eye only)	x	x	x	x	x	x	x	x	x	x	x		
Finger count, hand motion, light perception [l]	x	x	x	x	x	x	x	x	x	x	x		

g Laboratory evaluations included hematology, blood chemistry, and urinalysis.
h Obtained pre-treatment for both eyes and 60 minutes (±10 minutes) post-injection for study eye only.
i The measurement method used for a subject was to remain consistent throughout the study.
j Active (verteporfin) or sham (saline) PDT, if needed, was administered prior to ranibizumab/sham injection (all timepoints).
k Active (verteporfin) or sham (saline) PDT was administered based on need, as determined by assessment of fluorescein angiograms by the evaluating physician.

Study Period	Treatment Phase												Early Term.[a]
	Month												
	13	14	15	16	17	18	19	20	21	22	23	24	
Assessment Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	30±7
Vital Signs [m]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications [l, m]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events [c, m, n]	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact o	x	x	x	x	x	x	x	x	x	x	x	x	

l Injecting physician was to be performed within 15 minutes post-injection for study eye only.
m Performed post-treatment
n Adverse events were collected from Day 0 through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab should be followed, even after the subject's study participation is over, until the event resolves or the event is assessed as irreversible, chronic, or stable.
o Subjects were contacted 2 days (± 1 day) following treatment to elicit reports of any decreases in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Subjects were also asked whether they had taken the prescribed post-injection antimicrobials.

Table 6.1.3.2-5 Subject Disposition
Randomized Subjects

	Number of Subjects		
	Verteporfin PDT (n=143)	Ranibizumab 0.3 mg (n=140)	Ranibizumab 0.5 mg (n=140)
Completed Month 12 [a]	127 (88.8%)	128 (91.4%)	131 (93.6%)
Discontinued Treatment Prematurely	15 (10.5%)	14 (10.0%)	9 (6.4%)
Discontinued Study prematurely	10 (7.0%)	10 (7.1%)	5 (3.6%)
Safety Evaluable Population received study medication, as treated	143 (100%)	137 (97.9%)	140 (100%)
Intent-to-treat Population ≥ 1 on therapy study visit	143 (100%)	140 (100%)	140 (100%)
Per Protocol Population (for the analysis of 4 m BCVA at Month 12) No on-therapy study visits or protocol violation	114 (79.7%)	101 (72.1%)	103 (73.6%)
Excluded from PP Population	62 (26.1%)	38 (11.8%)	44 (18.3%)
Pharmacokinetic-Evaluable Population	136 (95.1%)	135 (96.4%)	137 (97.9%)

Note: Three subjects (301010, 345001, and 403004) in the 0.3 mg group did not receive any ranibizumab during the study.

Reviewer's Comment:
Overall, the study had good subject retention with 386 subjects completing Month 12 (91.3%).

The verteporfin PDT group (10.5%) and the ranibizumab 0.3 mg group (10.0%) had an almost equal number of subjects who discontinued treatment prior to Month 12. The ranibizumab 0.5mg group had the fewest subjects discontinue treatment at 6.4%.

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Table 6.1.3.2-6- Major Protocol Deviations during the First Treatment Year Randomized Subjects

Deviation	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=140)	Ranibizumab 0.5 mg (N=140)
Any deviation	**21 (14.7%)**	**36 (25.7%)**	**26 (18.6%)**
Treatment error: incorrect treatment	2 (1.4%)	7 (5.0%)	2 (1.4%)
Treatment error: received verteporfin PDT + ranibizumab at the same visit	0	2 (1.4%)	2 (1.4%)
Treatment error: incorrect administration	1 (0.7%)	3 (2.1%)	1 (0.7%)
Treatment error: received study drug kit from Study FVF2598G	0	3 (2.1%)	0
Treatment: off-schedule verteporfin/sham PDT	0	1 (0.7%)	1 (0.7%)
Treatment assignment unmasked	2 (1.4%)	1 (0.7%)	4 (2.9%)
Pre- and post-treatment procedure not followed	4 (2.8%)	9 (6.4%)	6 (4.3%)
Treatment holding criteria not followed	2 (1.4%)	1 (0.7%)	2 (1.4%)
Open-label verteporfin PDT in fellow eye <21 days after last ranibizumab/sham injection	5 (3.5%)	7 (5.0%)	3 (2.1%)
Open-label verteporfin PDT in fellow eye <5 days after last ranibizumab/sham injection	1 (0.7%)	2 (1.4%)	1 (0.7%)
Received excluded concomitant treatment in study eye	1 (0.7%)	0	0
Cataract surgery in the study eye within <28 days of a ranibizumab/sham injection	0	4 (2.9%)	1 (0.7%)
Visual acuity (4m) not assessed at Day 0 (study eye)	2 (1.4%)	7 (5.0%)	1 (0.7%)
Visual acuity (2 m) not assessed at Day 0 (study eye)	0	1 (0.7%)	1 (0.7%)
Visual acuity (2m) assessment incomplete; unknown if vision was better than 20/20 (study eye)	0	1 (0.7%)	0
Inconsistent method for measuring IOP	2 (1.4%)	2 (1.4%)	4 (2.9%)
Vital signs assessed predose	5 (3.5%)	3 (2.1%)	5 (3.6%)

Reviewer's Comments:

The most protocol deviations occurred in the ranibizumab 0.3 mg group (25.7%) followed by ranibizumab 0.5 mg (18.6%). Treatment errors, as a group, represented the majority of the protocol deviations in the ranibizumab 0.3 mg group.

The protocol deviations which occurred most frequently were the following: pre- and post-treatment procedures were not followed, open-label verteporfin PDT was administered in the fellow eye <21 days after the last ranibizumab/sham injection and vital signs were assessed pre-dose, not post-dose.

Table 6.1.3.2-7 Discontinued Subjects and Reason
Study FVF2587g

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
		Verteporfin PDT Group	
S08190	301006	Subject's Decision	25
S08201	306018	AE – COPD Exacerbation, Recurrent pneumonia	106
S08586	315004	AE – Lung cancer	191
S08187	316003	AE – Perforated gastric ulcer	211
S08214	321009	AE – Glioblastoma	177
S08146	326002	Subject's Decision – Decreasing vision	272
S08541	337006	Lost to follow-up	29
S08366	360002	AE – AMD requiring Macugen injxn, fellow eye	344
S08151	361001	Subject's Decision	130
S08314	364004	AE - Physician's Decision	302
S08221	368002	AE – Myocardial infarction	239
S02891	373001	AE – Bilateral blepharoconjunctivitis	3
S09325	381008	AE – Retinal detachment	211
S09311	384007	AE – Death, Cardiac arrest	121
S09339	403002	Lost to follow-up (after Month 8)	368
		0.3 mg Group	
S08190	301010	AE – Progression of AMD	1
S08220	302007	Non- compliance	271
S07441	303001	AE – Retinal detachment	58
S08214	321003	AE – Death, respiratory arrest	235
S08130	335004	AE – Blurred vision (unchanged VA)	361
S08541	337003	AE – Death, cardiac arrest	282
S07438	343005	AE – Lung cancer	278
S08222	344004	AE – Stroke	136
S08252	345001	Subject's Decision – never received treatment	7
S02201	352003	Subject's Decision – multiple medical problems	183
S08133	358003	AE – Recurrent CNVM, fellow eye	337
S08258	374003	AE – Death, viral infection	289
S09308	389003	Subject's Decision	182
S09339	403004	Physician's Decision – never received treatment	1
		0.5 mg Group	
S08220	302011	Lost to follow-up	180
S08165	317004	AE – Death, Congestive Heart Failure	219
S00444	319008	Subject's Decision	31
S08222	344005	AE – Progression of CNVM	175
S08234	349006	AE – Afferent pupillary defect	357
S08224	350004	Subject's Decision	212
S08083	369001	AE – Multiple infections	225
S09311	384003	AE – Death, cardiac failure	98
S09308	389001	AE – Severe uveitis	271

Reviewer's Comments:

Treatment discontinuations occurred at about the same frequency in the verteporfin PDT (15/143) and ranibizumab 0.3 mg group(14/140). In both groups, the reasons for discontinuation were most frequently adverse events due to systemic disease.

Table 6.1.3.1-8 Demographic Statistics by Treatment Group
Intent-to-Treat, Randomized Subjects

Demographic	Verteporfin PDT (n = 143)	Ranibizumab 0.3 mg (n = 140)	Ranibizumab 0.5 mg (n = 140)
Age (yr)			
Mean (SD)	77.7 (7.8)	77.4 (7.5)	76.0 (8.6)
Range	53-95	54-97	54-93
Age group (yr)			
50 to < 65	8 (5.6%)	9 (6.4%)	14 (10.0%)
65 to < 75	35 (24.5%)	28 (20.0%)	41 (29.3%)
75 to < 85	74 (51.7%)	84 (60.0%)	64 (45.7%)
≥ 85	26 (18.2%)	19 (13.6%)	21 (15.0%)
Sex			
Male	64 (44.8%)	73 (52.1%)	75 (53.6%)
Female	79 (55.2%)	67 (47.9%)	65 (46.4%)
Race/ethnicity			
White	140 (97.9%)	137 (97.9%)	136 (97.1%)
Black	1 (0.7%)	0	1 (0.7%)
Hispanic	1 (0.7%)	3 (2.1%)	2 (1.4%)
Other	1 (0.7%)	0	0
Any prior therapy for AMD	64 (44.8%)	63 (45.0%)	58 (41.4%)
Laser photocoagulation	19 (13.3%)	23 (16.4%)	20 (14.3%)
Medication / Supplements	52 (36.4%)	49 (35.0%)	46 (32.9%)

Reviewer's Comment:

The demographics of the subjects in the study were well balanced. The predominance of white elderly adults is representative of the population affected by this disease rather than a problem with enrollment.

Approximately 40% of subjects reported prior therapy for AMD in the study eye and approximately 15% reported prior laser photocoagulation in the study eye. No subjects had prior verteporfin PDT therapy because the study excluded it.

**Table 6.1.3.2-9 Baseline Ocular Characteristics in the Study Eye
Intent-to-Treat, Randomized Subjects**

Characteristics	Verteporfin PDT (n = 143)	Ranibizumab 0.3 mg (n = 140)	Ranibizumab 0.5 mg (n = 140)
Years since first diagnosis of neovascular AMD			
N	142	140	140
Mean (SD)	0.4 (0.9)	0.3 (0.6)	0.3 (0.6)
Range	0.0 – 5.4	0.0 – 5.4	0.0 - 7.3
Visual acuity at a starting test distance of 4 meters			
N	141	133	139
Number of letters (0–100)			
Mean (SD)	45.1 (15.2)	47.4 (13.7)	46.4 (14.8)
Range	3-73	1-74	0-75
≤ 44	62 (44.0%)	52 (39.1%)	57 (41.0%)
≥ 45	79 (56.0%)	81 (60.9%)	82 (59.0%)
Approximate Snellen equivalent			
Median	20/125	20/100	20/125
20/200 or worse	39 (27.7%)	37 (27.8%)	35 (25.2%)
Better than 20/200 but worse than 20/40	100 (70.9%)	92 (69.2%)	98 (70.5%)
20/40 or better	2 (1.4%)	4 (3.0%)	6 (4.3%)
Intraocular pressure (mmHg)			
N	143	140	140
Mean (SD)	15.2 (3.2)	15.2 (3.7)	15.4 (3.4)
Range	3–24	9–26	9–26
0–21	136 (95.1%)	133 (95.0%)	133 (95.0%)
22–29	7 (4.9%)	7 (5.0%)	7 (5.0%)

Reviewer's Comment:
The baseline ocular characteristics of the study eye were well balanced. The mean visual acuity ranged from 45.1 to 47.4 letters (Snellen equivalent 20/100 - 20/125) at a starting test distance of 4 meters.

Table 6.1.3.2-10 Fluorescein Angiography and Fundus Photography Characteristics of the Study Eye at Baseline Intent-to-Treat, Randomized Subjects

Characteristics	Verteporfin PDT (n = 141)	Ranibizumab 0.3 mg (n =140)	Ranibizumab 0.5 mg (n = 140)
CNV classification			
Predominantly classic	141 (98.6%)	134 (95.7%)	135 (96.4%)
Minimally classic	2 (1.4%)	5 (3.6%)	5 (3.6%)
Occult without classic	0	1 (0.7%)	0
Total area of lesion (DA)			
Mean (SD)	1.88 (1.40)	1.89 (1.44)	1.79 (1.54)
Range	0.07-5.75	0.12-7.20	0.05-10.00
≤ 2 DA	93 (65.0%)	98 (70.0%)	93 (66.4%)
>2 to 4 DA	34 (23.8%)	32 (22.9%)	34 (24.3%)
> 4 DA	16 (11.2%)	10 (7.1%)	13 (9.3%)
Total area of CNV (DA)			
Mean (SD)	1.48 (1.25)	1.48 (1.33)	1.31 (1.24)
Range	0.07-5.55	0.11-6.80	0.05-7.50
Area of classic CNV (DA)			
Mean (SD)	1.36 (1.13)	1.28 (1.05)	1.21 (1.12)
Range	0.07-5.55	0.00-6.40	0.05-5.30
Total area of leakage from CNV plus intense progressive RPE staining (DA)			
Mean (SD)	3.06 (1.81)	3.00 (1.92)	2.92 (2.08)
Range	0.20-8.20	0.20-11.00	0.25-9.00
Area of subretinal fluid (DA)[a]			
Mean (SD)	4.34 (2.15)	4.17 (2.43)	4.26 (2.53)
Range	0.00–9.00	0.00–14.00	0.00–12.00
Presence of occult CNV			
Absent	114 (79.7%)	107 (76.4%)	111 (79.3%)
Questionable	13 (9.1%)	12 (8.6%)	11 (7.9%)
Present	16 (11.2%)	21 (15.0%)	18 (12.9%)

a Subretinal fluid is also known as serous sensory retinal detachment. n=135 for the verteporfin PDT group, n=124 for the 0.3 mg group, and n=123 for the 0.5 mg group.

Reviewer's Comment:

There was no significant difference in the baseline characteristics of the CNV lesions across the treatment groups.

The vast majority of subjects had predominantly classic CNV lesions in each treatment group.

6.1.4 Efficacy Findings

6.1.4.1 Study FVF2598g Efficacy Results

The efficacy analysis was based on all randomized subjects with treatment groups as assigned, the intent-to-treat population with the LOCF method used to impute missing data. Some subjects did receive a treatment for which they were not randomized. These subjects were included in an "as treated" population in the safety analyses.

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint.

Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review, the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters not 2 meters.

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STUDY FVF2598g - PRIMARY EFFICACY RESULTS

Table 6.1.4.1-1
Proportion of Subjects Losing <15 Letters in Visual Acuity for the Study Eye at 12 Months Compared with Baseline at a Starting Distance of 4 Meters:

	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Randomized Subjects LOCF			
N	229	229	230
Responders[c]	138 (60.3%)	213 (93.0%)	209 (90.9%)
95% CI of the % [a]	(53.9%, 66.6%)	(89.7%, 96.3%)	(87.1%, 94.6%)
Difference in % (vs. sham) [b]		32.3%	29.9%
95% CI of the difference [b]		(25.3%, 39.4%)	(22.7%, 37.1%)
Per Protocol Subjects			
N	176	200	196
Responders[c]	106 (60.2%)	187 (93.5%)	181 (92.3%)
95% CI of the % [a]	(53.0%, 67.5%)	(90.1%, 96.9%)	(88.6%, 96.1%)
Difference in % (vs. sham) [b]		33.3%	32.1%
95% CI of the difference [b]		(25.3%, 41.3%)	(24.0%, 40.3%)

a By normal approximation; b Weighted estimates adjusting for the strata by using CMH weights; c From Cochran Chi Square tests adjusted for the strata (p<.0001).

Reviewer's Comment:
Based on the Hochberg-Bonferroni multiple comparison procedure defined within the protocol, the ranibizumab 0.3 mg and 0.5 mg doses demonstrate efficacy in this trial. The primary efficacy endpoint result for both ranibizumab groups is strongly statistically significant at p<0.0001 for each.

There is an approximate 30% treatment effect with both ranibizumab doses. At the 12 month primary efficacy endpoint, 93% of subjects in the ranibizumab 0.3-mg group and 90.9% of subjects in the ranibizumab 0.5-mg group lost fewer than 15 letters of vision from baseline compared with 60.3% of subjects in the sham injection group.

The number of subjects considered in each group was decreased in the Per Protocol analysis because some subjects did not have baseline visual acuity tested at 4 meters.

Table 6.1.4.1-2
Sensitivity Analysis of Visual Acuity for the Study Eye at 12 Months (Worst Outcome Imputation) at a Starting Distance of 4 Meters

	Sham (N=229)	Ranibizumab 0.3 mg (N=229)	Ranibizumab 0.5 mg (N=230)
Randomized Subjects LOCF			
N	229	229	230
Responders	118 (51.5%)	201 (87.8%)	194 (84.3%)
95% CI of the % [a]	(45.1%, 58.0%)	(83.5%, 92.0%)	(79.7%, 89.2%)
Difference in % (vs. sham) [b]		36.2%	32.8%
95% CI of the difference [b]		(28.5%, 44.0%)	(24.8%, 40.8%)
p-value (vs. sham) [c]		<0.0001	<0.0001

a By normal approximation; b Weighted estimates adjusting for the strata by using CMH weights; c From Cochran Chi Square tests adjusted for the strata.

Reviewer's Comment:
The statistically significant demonstration of efficacy is preserved with a greater than 30% treatment effect in the worst outcome imputation – sensitivity analysis.

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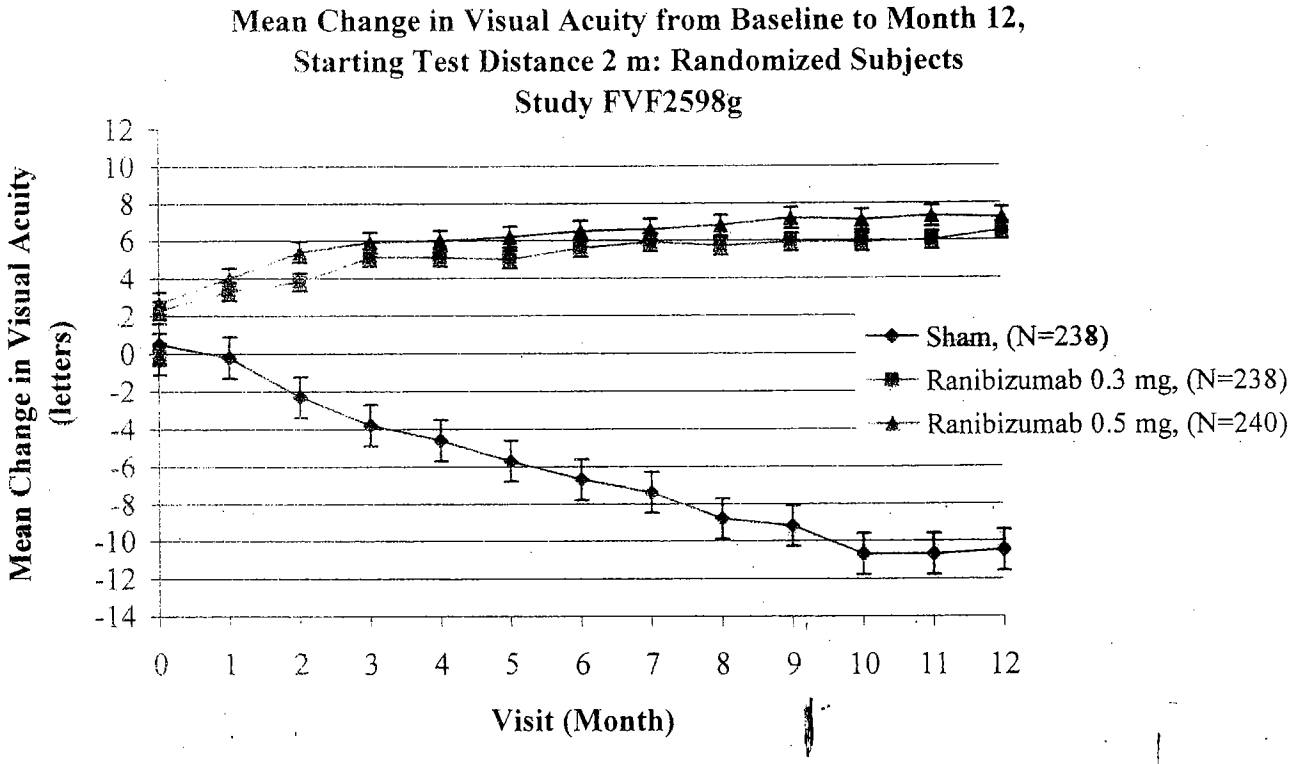
SECONDARY EFFICACY ENDPOINT RESULTS

Chart 6.1.4.1-1



Reviewer's Comment:

The difference in visual acuity mean change from baseline between each of the ranibizumab groups versus the sham injection group was statistically significant ($p<0.0001$) at each monthly assessment.

The Agency prefers that visual acuity testing be performed with at target distance of a minimum of 4 meters from the patient to minimize the potentially confounding influences of accommodation and patient positioning on the measurement. Visual acuity data with a starting test distance of 2 meters is presented here because visual acuity at a starting test distance of 4 meters was collected at baseline and Month 12 only in this study.

Table 6.1.4.1-3
Study Eye Visual Acuity Comparisons between Baseline and Month 12
Starting Test Distance of 4 meters: Randomized Subjects

Efficacy Variable	Response	Sham (N=229)	Ranibizumab 0.3 mg (N=229)	Ranibizumab 0.5 mg (N=230)
Gain of ≥ 15 letters from baseline	Yes	14 (6.1%)	42 (18.3%)	72 (31.3%)
Loss of <30 letters from baseline	Yes	193 (84.3%)	226 (98.7%)	226 (98.3%)
Mean change in visual acuity from baseline in ETDRS letters (SD)		-11.0 (17.9)	5.4 (13.4)	6.3 (14.1)
Number of Lines VA Change from Baseline		-2.2 (3.6)	1.1 (2.7)	1.4 (3.0)

Reviewer's Comment:
The differences were all statistically significant at the p<.0001 level. There appears to be a dose effect in the gain of ≥ 15 letters of vision from baseline, though this comparison was not a planned statistical comparison.

There is a statistically significant difference between sham and ranibizumab treatment groups in the prevention of vision loss defined as a loss of <30 letters. There is a statistically significant difference in the change in visual acuity from baseline, p<0.001, though this change is not considered clinically meaningful.

Table 6.1.4.1-4
Study Eye Visual Acuity at Month 12
Starting Test Distance of 4 meters
Randomized Subjects

Efficacy Variable	Response	Sham (N=237)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=240)
Mean Visual Acuity in ETDRS letters (SD)		42.5 (19.1)	58.8 (17.1)	59.9 (17.9)
Snellen Equivalent VA ≤ 20/200		102 (43.0%)	29 (12.2%)	28 (11.7%)

Reviewer's Comment:
There is a clinically meaningful and statistically significant (p<.0001) difference in mean visual acuity at Month 12 in ETDRS letters between the sham and ranibizumab treatment groups of 16 letters in the 0.3-mg group and 17 letters in the 0.5-mg group.

Table 6.1.4.1-5

Mean Change from Baseline in the Total Area of Lesion, Area of Classic CNV, and Area of Subretinal Fluid and the Proportion of Subjects with a Significant Growth of CNV in the Study Eye at 12 Months
Randomized Subjects

Change from Baseline at 12 Months	Sham (N=238)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=240)
Change in the total area of lesion (DA)			
N	238	238	240
Mean (SD)	2.33 (2.89)	0.11 (2.07)	0.14 (1.97)
Difference in LS means (vs. sham) [a]		-2.21	-2.18
Change in the area of classic CNV (DA)			
N [b]	87	86	91
Mean (SD)	0.79 (2.06)	-0.22 (0.44)	-0.23 (0.61)
Difference in LS means (vs. sham) [c]		-1.02	-1.02
Change in the area of SSR detachment/subretinal fluid			
N	220	218	218
Mean (SD)	1.08 (4.57)	-2.08 (4.31)	-2.62 (3.69)
Difference in LS means (vs. sham) [a]		-3.12	-3.66
Significant growth of CNV (≥ 0.3 DD increase)			
N	238	238	240
Mean (SD)	118 (49.6%)	31 (13.0%)	39 (16.3%)
Difference in LS means (vs. sham) [a]		-36.5%	-33.5%

NOTE: The LOCF method was used to impute missing data. Strata were defined using two factors: baseline CNV classification (minimally classic vs. occult without classic) and baseline visual acuity score (2 meters, ≤ 54 vs. ≥ 55 letters).
a Based on pairwise analysis of covariance models adjusted for the two stratification factors and baseline value of the endpoint ($p<.0001$). **b** Included subjects with minimally classic CNV at baseline only. **c** Based on pairwise analysis of covariance models adjusted for the baseline value of the endpoint and the baseline visual acuity category.

Reviewer's Comment:
Ranibizumab groups showed statistically significant differences when compared with the sham group ($p <0.0001$) in the mean change from baseline to 12 months in the total lesion area, the area of classic CNV, and the area of subretinal fluid. These differences are not necessarily clinically significant.

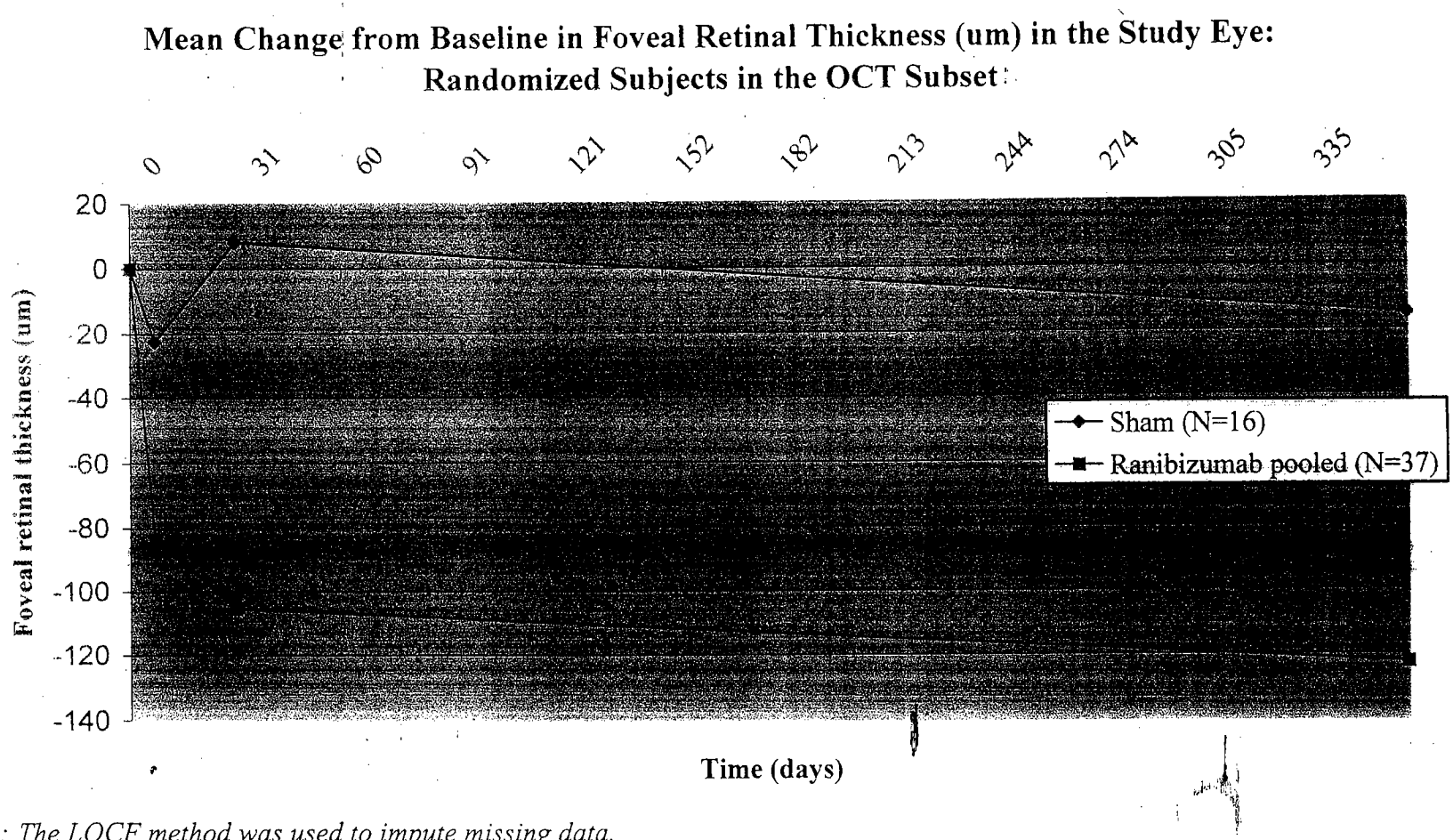
Table 6.1.4.1-6 Mean Change from Baseline in Retinal Thickness and Total Retinal Volume in the Study Eye at 12 Months: Randomized Subjects in the OCT Subset

Change from Baseline at 12 Months	Sham (N=16)	Ranibizumab pooled (N=37)
Foveal retinal thickness [c] (µm)		
N	15	31
Mean (SD)	-15.1 (131.6))	-122.5 (138.7)
Difference in LS means (vs. sham) [a]		-89.9
p-value (vs. sham) [a]		0.0088
Central retinal thickness [d] (µm)		
N	10	25
Mean (SD)	-1.8 (67.1)	-139.3 (113.9)
Difference in LS means (vs. sham) [a]		-103.2
p-value (vs. sham) [a]		0.0017
Total retinal volume (mm^3)		
N	10	23
Mean (SD)	-0.07 (0.82)	-1.42 (0.99)
Difference in LS means (vs. sham) [a]		-1.40
p-value (vs. sham) [a]		<0.0001

a Based on the analysis of covariance models adjusted for baseline value of the endpoint.
b Only the measurements based on the nominal scan diameter of 6.0 mm are included.
c Defined as the average thickness in microns of the center of the fovea based on the intersection of 6 radial line scans.
d Defined as the average retinal thickness in microns of the central retinal subfield (encompassing the foveal region) , which in turn is one of 9 subfields modeled after the ETDRS macular grid (central, four inner and four outer subfields).

Reviewer's Comment:
Within the subset of patients who were assessed with optical coherence tomography (OCT), the pooled ranibizumab group experienced statistically significant decreases in foveal retinal thickness, central retinal thickness and total retinal volume.

Chart 6.1.4.1-2

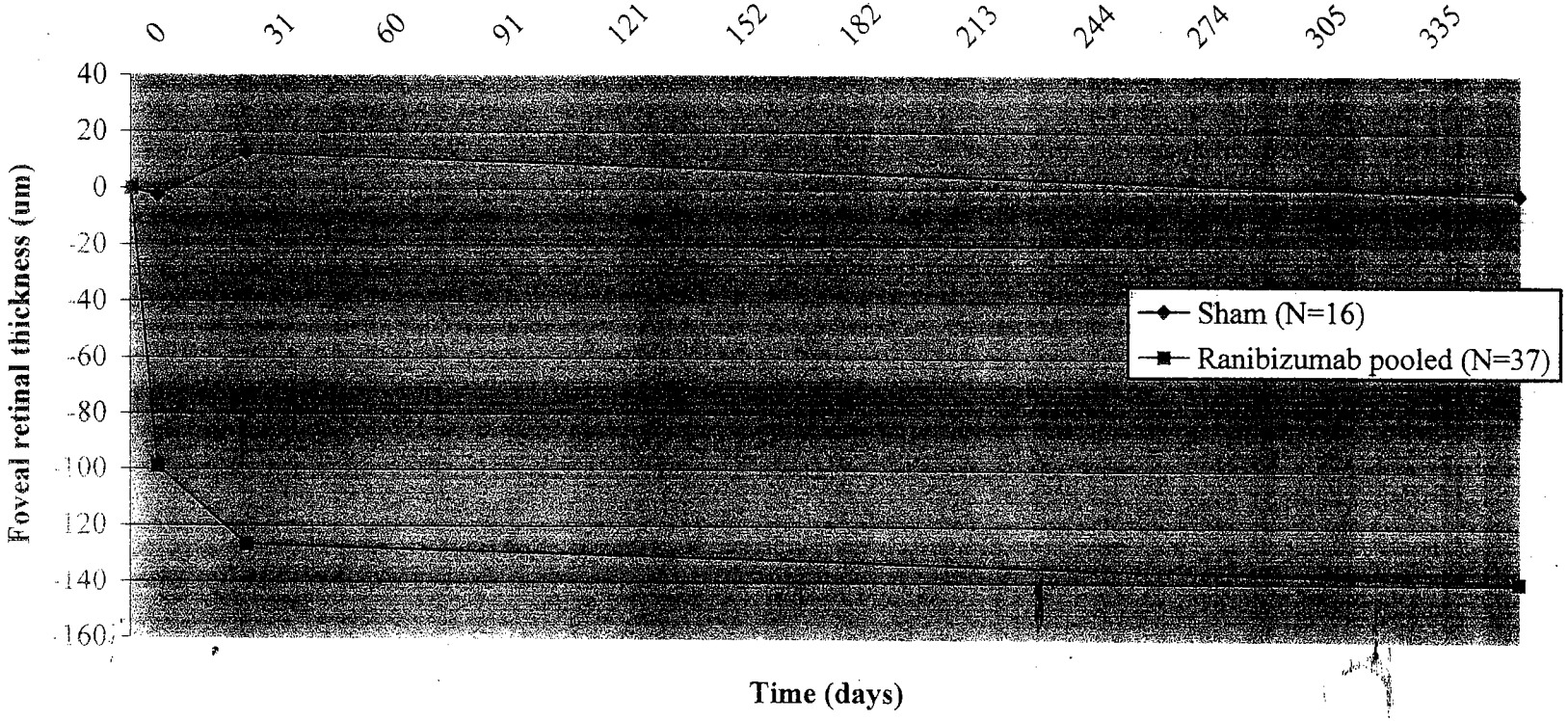


Note: The LOCF method was used to impute missing data.

Reviewer's Comment:
There is a statistically significant difference in foveal retinal thickness (μm) between the sham-injection group and pooled ranibizumab group at Month 1 ($p<0.0122$) and at Month 12 $p<0.0143$).

Chart 6.1.4.1-3

Mean Change from Baseline in Central Retinal Thickness (um) in the Study Eye: Randomized Subjects in the OCT Subset



Note: The LOCF method was used to impute missing data.

Reviewer's Comment:
There is a statistically significant difference in central retinal thickness (μm) between the sham-injection group and pooled ranibizumab group at Month 1 ($p<0.0002$) and at Month 12 $p<0.0012$).

SUBGROUP ANALYSES – PRIMARY EFFICACY VARIABLE

Table 6.1.4-6 Subgroup Analysis for the Proportion Losing <15 Letters in Visual Acuity in the Study Eye at 12 Months Compared with Baseline at a Starting Test Distance of 4 Meters: Randomized Subjects

Loss of <15 Letters From Baseline at Month 12 in the Study Eye	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
	Age < 75 Years			Age ≥ 75 Years		
N	73	75	75	156	154	155
n (%)	47 (64.4%)	70 (93.3%)	70 (93.3%)	91 (58.3%)	143 (92.9%)	139 (89.7%)
95% CI of the %	(53.4%, 75.4%)	(87.7%, 99.0%)	(87.7%, 99.0%)	(50.6%, 66.1%)	(88.8%, 96.9%)	(84.9%, 94.5%)
Difference in % (vs. Sham)		28.9%	28.9%		34.5%	31.3%
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	Female			Male		
N	152	148	148	79	81	82
n (%)	90 (59.2%)	139 (93.9%)	135 (91.2%)	48 (62.3%)	74 (91.4%)	74 (90.2%)
95% CI of the %	(51.4%, 67.0%)	(90.1%, 97.8%)	(86.7%, 95.8%)	(51.5%, 73.2%)	(85.2%, 97.5%)	(83.8%, 96.7%)
Difference in % (vs. Sham)		34.7 %	32.0%		29.0%	27.9%
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	≤ 54 Letters			≥ 55 Letters		
N	103	110	114	126	119	116
n (%)	74 (71.8%)	104 (94.5%)	108 (94.7%)	64 (50.8%)	74 (91.4%)	74 (90.2%)
95% CI of the %	(63.2%, 80.5%)	(90.3%, 98.8%)	(90.6%, 98.8%)	(42.1%, 59.5%)	(86.6%, 96.6%)	(81.0%, 93.2%)
Difference in % (vs. Sham)		22.7 %	22.9%		40.8%	36.3%
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001

Loss of < 15 Letters from Baseline at Month 12 in the Study Eye	Sham	Ranibizumab		Sham	Ranibizumab	
		0.3 mg	0.5 mg		0.3 mg	0.5 mg
	Minimally Classic CNV at Baseline			**Occult with No Classic CNV at Baseline**		
N	80	85	88	149	143	141
n (%)	51 (63.8%)	79 (92.9%)	81 (92.0%)	87 (58.4%)	133 (93.0%)	127 (90.1%)
95% CI of the %	(53.2%, 74.3%)	(87.5%, 98.4%)	(86.4%, 97.7%)	(50.5%, 66.3%)	(88.8%, 97.2%)	(85.1%, 95.0%)
Difference in % (vs. Sham)		29.2 %	28.3 %		34.6 %	31.7 %
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	Baseline Lesion Size ≤ 4 DA			**Baseline Lesion Size > 4 DA**		
N	119	130	119	110	99	111
n (%)	72 (60.5%)	121 (93.1%)	81 (92.0%)	66 (60.0%)	192 (92.9%)	98 (88.3%)
95% CI of the %	(51.7%, 69.3%)	(88.7%, 97.4%)	(88.8%, 97.8%)	(50.8%, 69.2%)	(87.9%, 98.0%)	(82.3%, 94.3%)
Difference in % (vs. Sham)		32.6 %	32.8 %		32.9 %	28.3 %
p-value (vs. sham)		<0.0001	<0.0001		<0.0001	<0.0001
	With Prior Laser Photocoagulation			**With No Prior Laser Photocoagulation**		
N	20	12	14	209	217	216
n (%)	10 (50.0%)	12 (100.0%)	13 (92.9%)	128 (61.2%)	201 (92.6%)	196 (90.7%)
95% CI of the %	(28.1%, 71.9%)	(100%, 100%)	(79.4%, 100%)	(54.6%, 67.8%)	(89.1%, 96.1%)	(86.9%, 94.6%)
Difference in % (vs. Sham)		50.0 %	42.9 %		31.4 %	29.5 %
p-value (vs. sham)		0.0040	0.0068		<0.0001	<0.0001

Reviewer's Comment:

The approximately 30% treatment effect was maintained and was statistically significant to the p<0.0001 level in all except for a few subgroups which had small numbers of subjects. In patients with baseline visual acuity of ≤ 54 Letters, the treatment effect was approximately 22%.

There was a small number of patients in the prior laser photocoagulation subgroup (N=35). The treatment effect was higher in this subgroup with the Ranibizumab 0.3 mg dose, 50.0% (p=0.0040) than with the Ranibizumab 0.5 mg dose, 42.9% (p=0.0068).

6.1.4.2 Study FVF2587g – Primary Efficacy Results

The efficacy analysis was based on all randomized subjects with treatment groups as assigned, the intent-to-treat population with the LOCF method used to impute missing data. Some subjects did receive a treatment for which they were not randomized.

Reviewer's Comment:

As noted in Section 2.5 regarding previous correspondence and meetings, the Agency does not agree with the sponsor's primary efficacy endpoint. Visual acuity testing is recommended to be performed with at target distance of a minimum of 4 meters from the patient. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement.

For the purposes of this review the Agency will consider the primary efficacy endpoint as the proportion of subjects with a loss of fewer than 15 letters in the visual acuity score in the study eye at 12 months compared with baseline, based on assessments at a starting test distance of 4 meters not 2 meters.

STUDY FVF2587g - PRIMARY EFFICACY RESULTS

Table 6.1.4.2-1
Proportion of Subjects Losing <15 Letters in Visual Acuity for the Study Eye at 12 Months Compared with Baseline at a Starting Distance of 4 Meters: Randomized Subjects

	Verteporfin PDT n=143	Ranibizumab 0.3 mg n=140	Ranibizumab 0.5 mg n=140
Randomized Subjects LOCF			
N	141	133	139
Responders	93 (66%)	126 (94.7%)	136 (97.8%)
95% CI of the % [a]	(58.1%, 73.8%)	(90.9%, 98.5%)	(95.4%, 100%)
Difference in % (vs. verteporfin PDT) [b]		29.0%	32.1%
95% CI of the difference [b]		(20.4%, 37.6%)	(24.0%, 40.2%)
Non-inferiority test			
One-sided (1- α) 100% CI of the difference (vs. verteporfin PDT) [b, c]		(20.4%, --)	(23.9%, --)
p value (vs. verteporfin PDT) [d, e]		<0.0001	<0.0001

Note: Strata were defined using baseline visual acuity score (4 meters, ≤44 vs. ≥45 letters).
a By normal approximation; **b** Weighted estimates adjusting for the strata by using CMH weights and normal approximation of the weighted estimates; **c** α=0.0246.; **d** From normal approximation tests adjusted for the strata.; **e** From Cochran Chi Square tests adjusted for the strata

Table 6.1.4.2-2

Proportion of Subjects Losing <15 Letters in Visual Acuity for the Study Eye at 12 Months Compared with Baseline at a Starting Distance of 4 Meters: Per-Protocol Subjects

	Verteporfin PDT n=114	Ranibizumab 0.3 mg n=140	Ranibizumab 0.5 mg n=140
Per-Protocol Subjects Observed Cases Only			
N	114	101	103
Responders	70 (61.4%)	95 (94.1%)	100 (97.1%)
95% CI of the % [a]	(52.5%, 70.3%)	(89.4%, 98.7%)	(93.8%, 100%)
Difference in % (vs. verteporfin PDT) [b]		32.7%	35.7%
95% CI of the difference [b]		(22.6%%, 42.7%)	(26.2%, 45.2%)
Non-inferiority test			
One-sided (1- α) 100% CI of the difference (vs. verteporfin PDT) [b, c]		(23.2%, --)	(26.4%, --)
p-value (vs. verteporfin PDT) [d,e]		<0.0001	<0.0001

Note: Observed cases only. Strata were defined using baseline visual acuity score (4 meters, ≤44 vs. ≥45 letters).
a All tests and CIs are two-sided (except non-inferiority tests) and based on pairwise models. b Based on normal approximation for binomial proportions. c α=0.0246 d From normal approximation tests adjusted for the strata.;
e From Cochran Chi Square tests adjusted for the strata

Reviewer's Comment:

The number of subjects considered in each group was slightly decreased because baseline visual acuity at a starting test distance of 4 meters was not obtained in all subjects.

Based on the pre-specified criteria for assessing significance, the ranibizumab 0.3 mg and 0.5 mg doses demonstrate efficacy in this trial. The primary efficacy endpoint result for both ranibizumab groups is highly statistically significant at p<0.0001 for each dose for the Intent-to-Treat and Per Protocol populations.

There is an approximate 30% treatment effect with both doses. At the 12 month primary efficacy endpoint, 94.1% of subjects in the Ranibizumab 0.3-mg group and 97.1% of subjects in the Ranibizumab 0.5-mg group lost fewer than 15 letters of vision from baseline compared with 61.4% of subjects in the verteporfin PDT group. The favorable treatment effect of each of the ranibizumab doses over the verteporfin PDT group was statistically significant, p<0.0001.

For each ranibizumab dose, the lower limit of the one-sided CI (at α=0.0246) for the difference in the percentage from the verteporfin PDT group far exceeded the pre-specified non-inferiority limit of -7%, and the non-inferiority test was statistically significant, p<0.0001.

Table 6.1.4.2-3
Sensitivity Analysis of Visual Acuity
In the Study Eye at Month 12
(Worst Outcome Imputation) at a Starting Distance of 4 Meters

Primary Efficacy Variable: Loss of <15 Letters from Baseline	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=140)	Ranibizumab 0.5 mg (N=140)
Randomized Subjects with FA			
N	141	133	139
Responders	79 (56.0%)	113 (85.0%)	122 (87.8%)
95% CI of the % [a]	(47.8%, 64.2%)	(78.9%, 91.0%)	(82.3%, 90.5%)
Difference in % (vs. Verteporfin PDT) [b]		28.9%	31.7%
95% CI of the difference [b]		(18.7%, 39.1%)	(21.9%, 41.6%)
Non-inferiority test			
One-sided (1- α) 100% CI of the difference (vs. verteporfin PDT) [b, c]		(19.1%, --)	(22.2%, --)
p-value (vs. Verteporfin PDT) [d,e]		<0.0001	<0.0001

Note: Observed cases only. Strata were defined using baseline visual acuity score (4 meters, ≤44 vs. ≥45 letters).
a All tests and CIs are two-sided (except non-inferiority tests) and based on pairwise models. **b** Based on normal approximation for binomial proportions. **c** α=0.0246 **d** From normal approximation tests adjusted for the strata.; **e** From Cochran Chi Square tests adjusted for the strata

Reviewer's Comment:
The statistically significant demonstration of efficacy is preserved in the worst outcome imputation – sensitivity analysis. The treatment effect of approximately 30% is preserved in both the intent-to-treat and per protocol populations.

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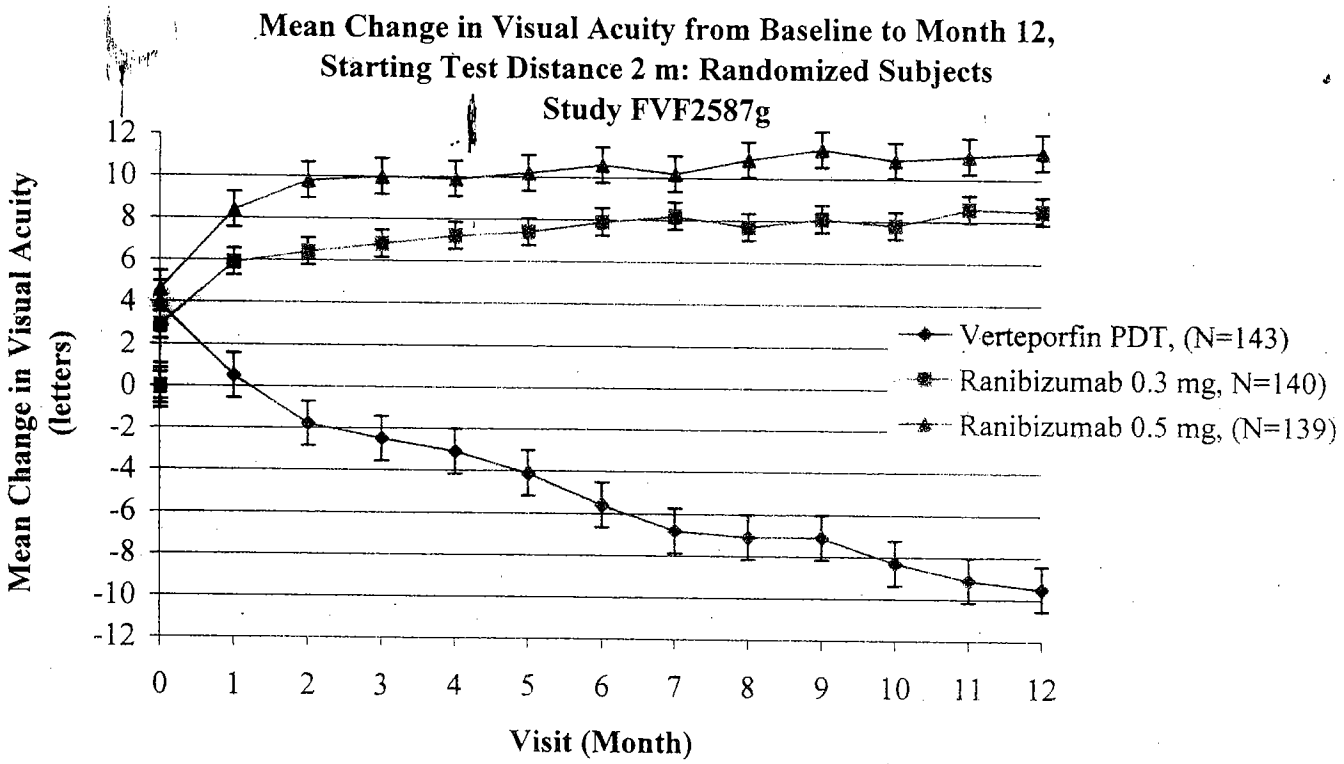
SECONDARY EFFICACY ENDPOINT RESULTS

Chart 6.1.4.2-1



Reviewer's Comment:
The difference in mean change from baseline in visual acuity between each of the ranibizumab groups versus the verteporfin PDT group was highly statistically significant ($p<0.001$) at each monthly assessment.

Table 6.1.4.2-4
Study Eye Visual Acuity Comparisons between Baseline and Month 12
Starting Test Distance of 4 meters
Randomized Subjects

Efficacy Variable	Response	[redacted]	Ranibizumab 0.3 mg (N=140)	Ranibizumab 0.5 mg (N=140)
Gain of ≥ 15 letters from baseline		N=141	N=133	N=139
	Yes	15 (10.6%)	37 (27.8%)	51 (36.7%)
Loss of <30 letters from baseline		N=141	N=133	N=139
	Yes	125 (88.7%)	131 (98.5%)	139 (100%)
Mean change in visual acuity from baseline in ETDRS letters (SD)		N=141	N=133	N=139
		-8.5 (17.8)	7.2 (15.3)	11.0 (15.8)
Number of Lines VA Change from Baseline Mean (SD)		N=141	N=133	N=139
		-1.7 (3.6)	1.5 (3.1)	2.3 (3.3)

p<.0005 for all comparisions to sham

Reviewer's Comment:

A clinically meaningful and statistically significant gain in 15 letters of vision was noted in the 0.3 mg ranibizumab group and the 0.5 mg group, 27.8% and 36.7%, respectively when compared to the verteporfin PDT treatment group, 10.6%. There appears to be a dose effect in this increase in vision though this comparison was not a planned statistical comparison.

There is a statistically significant difference between verteporfin PDT and ranibizumab treatment groups in the prevention of vision loss of <30 letters.

There is a statistically significant difference in the change in visual acuity from baseline though this change is not considered clinically meaningful.

Table 6.1.4-5
Study Eye Visual Acuity at Month 12
Starting Test Distance of 4 meters
Randomized Subjects

Efficacy Variable		[illegible]	Ranibizumab	
			0.3 mg (N=238)	0.5 mg (N=240)
Mean Visual Acuity at Month 12 in ETDRS letters (SD)		N=143	N=139	N=140
		36.3 (16.6)	54.6 (19.1)	57.6 (18.6)
	p-value	--	<0.0001	<0.0001
Snellen Equivalent VA of 20/200 or Worse		N=143	N=139	N=140
		81 (56.6%)	32 (23.0%)	23 (16.4%)
	p-value	--	<0.0001	<0.0001

Reviewer's Comment:

There is a clinically meaningful and statistically significant difference in the mean visual acuity at Month 12 between the verteporfin PDT and ranibizumab 0.5- mg treatment group. The difference between the verteporfin PDT and ranibizumab 0.3-mg is statistically significant and approaches a clinically relevant result.

There is a statistically significant difference in the number of patients with Snellen equivalent visual acuity of 20/200 or worse between the sham and ranibizumab treatment groups.

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Table 6.1.4.2-6

Mean Change from Baseline in the Total Area of Lesion, Area of Classic CNV, and Area of Subretinal Fluid and the Proportion of Subjects with a Significant Growth of CNV in the Study Eye at 12 Months
Randomized Subjects

Change from Baseline at Month 12	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=140)	Ranibizumab 0.5 mg (N=140)
Change in the total area of lesion (DA)			
N	143	140	140
Mean (SD)	2.56 (3.09)	0.36 (1.06)	0.28 (1.29)
Difference in LS means (vs. verteporfin PDT) [b]		-2.20	-2.30
Change in total area of CNV [d] (DA)			
N [b]	143	140	140
Mean (SD)	1.63 (2.27)	0.20 (0.97)	0.22 (1.25)
Difference in LS means (vs. verteporfin PDT) [b]		-1.42	-1.45
Change in the area of subretinal fluid [c]			
N	135	124	123
Mean (SD)	-0.58 (4.02)	-2.68 (2.74)	-.3.39 (2.90)
Difference in LS means (vs. verteporfin PDT) [b]		-2.23	-2.89
Significant growth of CNV (≥ 0.3 DD increase)			
N	143	140	140
Mean (SD)	84 (58.7%)	30 (21.4%)	38 (27.1%)
Difference in % (vs. verteporfin PDT) [e,f]		-37.3%	-31.7%

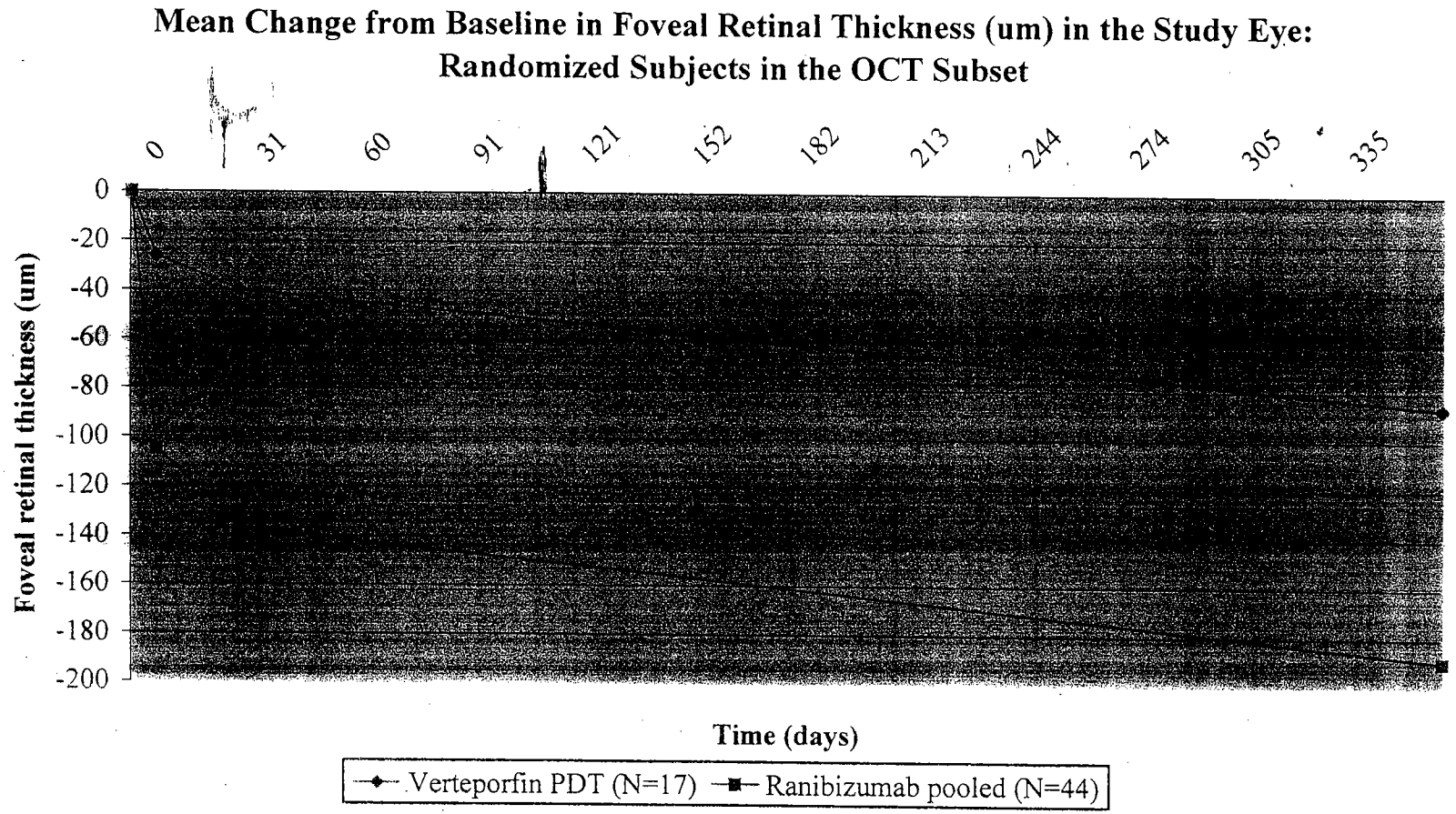
NOTE: The LOCF method was used to impute missing data. Strata were defined using baseline visual acuity score (2 meters, ≤ 44 vs. ≥ 45 letters).

a Based on t-distribution. **b** Based on pairwise analysis of covariance models adjusted for the stratification variable and baseline value of the corresponding endpoint. **c** Subretinal fluid is also known as serous sensory retinal detachment. **d** 95-95% of subjects had predominantly classic lesions. 85-92% of each CNV was classic in type. **e** Weighted estimates adjusting for the strata by using the CMH weights and normal approximation of the weighted estimates. **f** From Cochran chi square tests adjusted for the strata

Reviewer's Comment:

Ranibizumab groups showed highly statistically significant differences with the verteporfin PDT group (p <0.0001) in the mean change from baseline at 12 months in the total lesion area, total area of CNV, area of subretinal fluid and in the growth of CNV.

Chart 6.1.4.2-2



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Note: The LOCF method was used to impute missing data.

Reviewer's Comment:

There is a statistically significant difference in foveal retinal thickness (μm) between the verteporfin PDT group and pooled ranibizumab group at Month 1 ($p<0.0045$) and at Month 12 $p<0.0004$).

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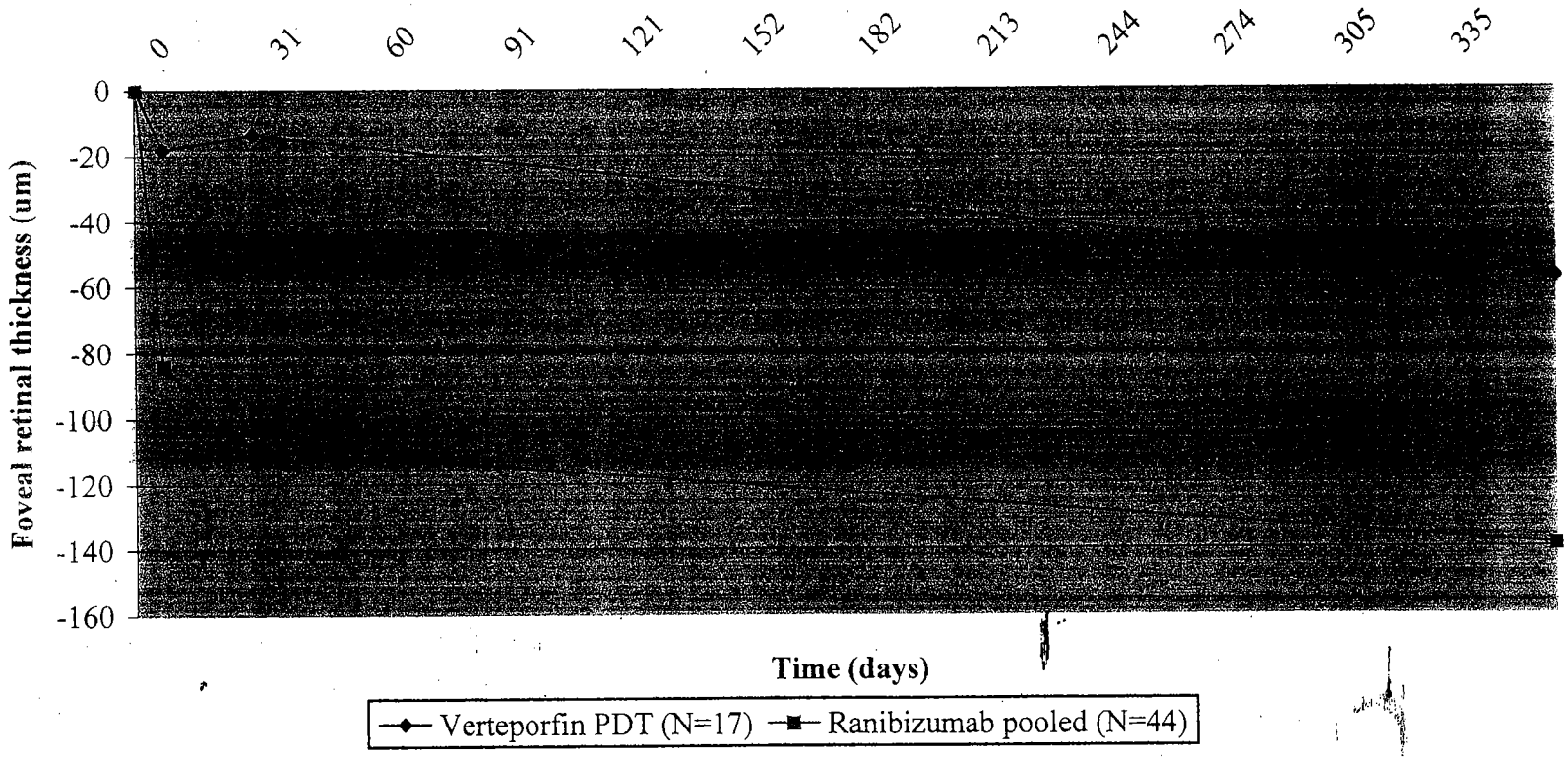
Chart 6.1.4.2-3

Mean Change from Baseline in Central Retinal Thickness (um) in the Study Eye: Randomized Subjects in the OCT Subset



Note: The LOCF method was used to impute missing data.

Reviewer's Comment:
There is a statistically significant difference in central retinal thickness (μm) between the verteporfin PDT group and pooled ranibizumab group at Month 1 ($p<0.0009$) and at Month 12 $p<0.0527$).

SUBGROUP ANALYSES – PRIMARY EFFICACY VARIABLE

Table 6.1.4.2-7 Subgroup Analysis for the Proportion Losing <15 Letters in Visual Acuity in the Study Eye at 12 Months Compared with Baseline at a Starting Test Distance of 4 Meters: Randomized Subjects

Loss of < 15 Letters from Baseline at Month 12 in the Study Eye	Verteporfin PDT	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg	Verteporfin PDT	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
	Age < 75 Years			**Age ≥ 75 Years**		
N	43	37	55	99	97	85
n (%)	26 (61.9%)	35 (91.2%)	53 (98.1%)	67 (67.7%)	91 (93.8%)	83 (97.6%)
95% CI of the %	(47.2%, 76.6%)	(91.9%, 100%)	(94.6%, 100%)	(58.5%, 76.9%)	(89.0%, 98.6%)	(94.4%, 100%)
Difference in % (vs. PDT)		35.3%	36.2%		26.1%	30.0%
	Female			**Male**		
N	78	64	64	63	69	75
n (%)	51 (65.4%)	61 (95.3%)	63 (98.4%)	42 (66.7%)	65 (64.2%)	73 (97.3%)
95% CI of the %	(54.8%, 75.9%)	(90.1%, 100%)	(95.4%, 100%)	(55.0%, 78.3%)	(88.7%, 99.7%)	(93.7%, 100%)
Difference in % (vs. PDT)		29.9 %	33.1%		27.5%	30.7%
	≤ 44 Letters			**≥ 45 Letters**		
N	65	58	60	76	75	78
n (%)	49 (75.4%)	55 (94.8%)	58 (96.7%)	44 (57.9%)	71 (94.7%)	77 (98.7%)
95% CI of the %	(64.9%, 85.9%)	(89.1%, 100%)	(92.1%, 100%)	(46.8%, 69.0%)	(89.6%, 99.8%)	(96.2%, 100%)
Difference in % (vs. PDT)		19.4 %	21.3%		36.8%	40.8%
	Occult CNV Present at Baseline			**Occult CNV Absent at Baseline**		
N	16	17	18	125	116	121
n (%)	7 (43.8%)	15 (88.2%)	18 (100%)	86 (68.8%)	111 (95.7%)	118 (97.5%)

Loss of < 15 Letters from Baseline at Month 12 in the Study Eye	Verteporfin PDT	Ranibizumab		Verteporfin PDT	Ranibizumab	
		0.3 mg	0.5 mg		0.3 mg	0.5 mg
95% CI of the %	(19.4%, 68.1%)	(72.9%, 100%)	(100%, 100%)	(60.7%, 76.9%)	(92.9%, 99.4%)	(94.8%, 100%)
Difference in % (vs. PDT)		44.5 %	56.3 %		26.9 %	28.7 %
p-value (vs. PDT)		0.0067	0.0002		<0.0001	<0.0001
	Baseline Lesion Size ≤ 4 DA			**Baseline Lesion Size > 4 DA**		
N	125	124	126	16	9	13
n (%)	82 (65.6%)	117 (94.4%)	124 (98.4%)	11 (68.8%)	9 (100%)	12 (92.3%)
95% CI of the %	(57.3%, 73.9%)	(90.3%, 98.4%)	(96.2%, 100%)	(46.0%, 91.5%)	(100%, 100%)	(77.8%, 100%)
Difference in % (vs. PDT)		28.8 %	32.8 %		31.3 %	23.6 %
p-value (vs. PDT)		<0.0001	<0.0001		0.0608	0.1194
	With Prior Laser Photocoagulation			**With No Prior Laser Photocoagulation**		
N	19	19	20	122	114	119
n (%)	11 (57.9%)	19 (100.0%)	20 (100%)	82 (67.2%)	107 (93.9%)	116 (97.5%)
95% CI of the %	(35.7%, 80.1%)	(100%, 100%)	(100%, 100%)	(58.9%, 75.5%)	(89.5%, 98.3%)	(94.7%, 100%)
Difference in % (vs. PDT)		42.1 %	42.1 %		26.6 %	30.3 %
p-value (vs. PDT)		0.0015	0.0011		<0.0001	<0.0001

Note: The LOCF was used to impute missing data. The 95% CIs were based on normal approximation. p-values were from the Pearson Chi Square test.

Reviewer's Comment:

The approximately 30% treatment effect was maintained and was statistically significant to the p<0.0001 level in all except for a few subgroups likely due to the small number of subjects in those subgroups.

In patients with a baseline lesion size of > 4 disc areas, only the ranibizumab 0.3-mg dose achieved statistical significance versus verteporfin PDT, p=0.0242, perhaps due to the small number of subjects or worse disease. In this subgroup, the ranibizumab pooled group was significant with a p-value of 0.0199. Similar results were seen in the subgroups with occult CNV present at baseline and with prior laser photocoagulation.

6.1.5 Clinical Microbiology

This is not an antimicrobial. Not applicable.

6.1.6 Efficacy Conclusions

The submitted Phase 3 studies in BLA 125156 Lucentis (ranibizumab injection) demonstrate the efficacy for the use of ranibizumab 0.5-mg in the treatment of neovascular age-related macular degeneration.

These studies both demonstrated an approximately 30% treatment effect of ranibizumab 0.3-mg and 0.5-mg compared to sham and verteporfin PDT, respectively, for the primary efficacy endpoint, the proportion of subjects with a loss of fewer than 15 letters in the best corrected visual acuity score at Month 12 compared with baseline.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Phase 3 studies presented in this Biologics License Application, FVF2587g and FVF2598g, included 754 safety evaluable patients. In Study FVF2598g, subjects were followed monthly from Day 0 through Month 12 and received an average 12 of a total 13 possible intravitreal ranibizumab injections. The number of treatments received was slightly lower for the sham-injection group compared with the ranibizumab groups. There was no imputation of missing values due to patient discontinuation or missed visits performed in the safety data set. In Study FVF2587g, subjects were followed monthly as well. The mean number of injections in the ranibizumab and sham intravitreal injection groups was approximately 12 for each group.

Safety was assessed through the summary of ocular and non-ocular adverse events, serious adverse events, ocular assessments, deaths, laboratory test results, vital signs, and antibodies to ranibizumab. Safety analyses included all subjects who received at least one ranibizumab or sham injection. Unless specified otherwise, safety analyses were performed for the safety-evaluable subjects. Subjects were analyzed according to the actual treatment received. Safety summaries for this Clinical Study Report include data from the first treatment year.

In Study FVF2598g, the safety evaluable population was defined as randomized subjects who received at least one treatment with study drug. Treatment group assignment as follows:

- Sham: subjects randomized to the sham-injection group who received a sham injection on Day 0
- 0.3 mg Ranibizumab: subjects randomized to receive 0.3 mg ranibizumab or subjects who were randomized to sham but received a 0.3 mg injection of ranibizumab on Day 0 in error
- 0.5 mg Ranibizumab: subjects randomized to receive 0.5 mg ranibizumab or subjects who were randomized to sham but received a 0.5 mg injection of ranibizumab on Day 0 in error

In Study FVF2587g, the safety-evaluable population was defined as randomized subjects who received at least one of the following treatments: ranibizumab injection, sham intravitreal injection, active verteporfin PDT, or sham PDT with saline. Treatment groups for this population were defined according to the actual treatment received during the first treatment year.

- If a subject received only one type of active treatment (verteporfin PDT, 0.3 mg ranibizumab or 0.5 mg ranibizumab), regardless of any sham PDT or sham intravitreal injections received, the subject's treatment group was the active treatment received.
- If a subject received a combination of different active treatments, regardless of any sham PDT or sham intravitreal injections received, and one of the active treatments received

was the treatment the subject was randomized to, the subject's treatment group was as randomized.

- If a subject received a combination of different active treatments, regardless of any sham PDT or sham intravitreal injection received, and none of the active treatments received was the treatment the subject was randomized to, the subject's treatment group was the first active treatment received.
- If a subject did not receive any active treatment but received any combination of sham PDT or sham intravitreal injection, the subject's treatment group was as randomized.

In Study FVF2598g, the most common ocular adverse events in the study eye reported more frequently in each of the ranibizumab groups than in the corresponding control groups in both studies were conjunctival hemorrhage, eye pain, increased IOP, retinal disorder, and vitreous floaters. Many of these adverse advents appear to be related to the conjunctival anesthetic or intravitreal injection procedures.

Key serious ocular adverse events of endophthalmitis, intraocular inflammation, retinal detachment, retinal tear, increased IOP, and traumatic cataract were all uncommon in ranibizumab-treated subjects (reported in < 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).

A trend in intraocular inflammation adverse events was observed, with rates of approximately 10%–15% in the ranibizumab groups compared with rates of approximately 3% or 10% in the verteporfin PDT or sham-control groups, respectively. However, the reported intraocular inflammation adverse events were generally mild in severity. The incidence of intraocular inflammation adverse events was consistent with the results based on slitlamp examination.

As expected with a drug injected intravitreally, there was a small trend in increased IOP adverse events toward higher rates in the ranibizumab groups than in the control groups, with no difference in frequency or severity observed between the two doses. Most of these events were mild to moderate in severity.

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7.1.1 Deaths

Three deaths occurred during the first treatment year of Study FVF2598g. One subject in the 0.3 mg ranibizumab group died from a heart attack. The other two subjects were both in the ranibizumab 0.5 mg group; 1 subject died as a result of a small bowel infarct and the other died from chronic asthma / chronic obstructive pulmonary disease (COPD).

Seven deaths occurred during the first treatment year of Study FVF2587g.

Table 7.1.1-1 Deaths Occurring during Phase 3 Studies

Primary Cause of Death	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=240	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
Total	**0**	**1 (0.4%)**	**2 (0.8%)**	**2 (1.4%)**	**3 (2.2%)**	**2 (1.4%)**
Cardiac Arrest	0	0	0	1(0.7%)	1 (0.7%)	0
Cardiac Failure	0	0	0	0	0	1 (0.7%)
COPD	0	0	1 (0.4%)	1 (0.7%)	0	0
Myocardial infarction	0	1 (0.4%)	0			
Respiratory Arrest	0	0	0	0	1 (0.7%)	0
Small bowel infarct	0	0	1 (0.4%)			
Viral Syndrome	0	0	0	0	1 (0.7%)	0
Worsened of chronic CHF	0	0	0	0	0	1 (0.7%)

Reviewer's Comment:
There were considerably more deaths in the FVF2587g trial though there were no imbalances in the causes or association to treatment noted.

The deaths were not considered to be related to therapy.

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7.1.2 Other Serious Adverse Events

Table 7.1.2-1 Study FVF2598g
Serious Ocular Adverse Events in the Study Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
		Sham Group		
S08215	104005	30 letter loss of vision	99	None
S08087	105001	Serous hemorrhagic macular detachment	305	None
S07441	107003	Subretinal hemorrhage	63	Dose held
S08216	108006	30 letter loss of vision - Worsened CNV	246	None
S08201	118004	Cerebrovascular accident	319	None
S08130	125006	30 letter loss of vision – Worsened AMD	32	None
S08220	143005	30 letter loss of vision – Worsened AMD	239	Dose held
S08212	144002	30 letter loss of vision – Worsened AMD	94	Dose held, PDT
S08366	148001	30 letter loss of vision – Worsened AMD	155	Dose held
S08133	164002	Progression of AMD	57	Dose held, D/C study
S02796	185005	30 letter loss of vision – Worsened AMD	127	None
S02201	188006	30 letter loss of vision – Worsened AMD	62	None
		0.3 mg Group		
S07348	101001	30 letter loss of vision – Worsened AMD	126	None
S08127	102005	30 letter loss of vision	122	Dose held
S08217	123002	Iridocyclitis	33	None
S06531	126002	Retinal tear	58	Dose held, Procedure
S08246	131003	30 letter loss of vision - Subretinal fibrosis	127	None
S08246	131013	Increased intraocular pressure	239	None
S08208	141014	30 letter loss of vision –Vit. hemorrhage	84	Dose held
S08220	143011	Endophthalmitis	270	Meds / Surgery
	143018	30 letter loss of vision – Worsened AMD	60	None
S08189	160001	Iridocyclitis	94	Study drug d/ced
S00399	162002	Retinal hemorrhage, Depression	15	D/C Study
S08131	179002	30 letter loss of vision – Worsened AMD	148	None
S08125	183001	30 letter loss of vision – Worsened AMD	183	None
S08165	184001	RPE Tear / Detachment	30	None
S08252	193001	Corneal abrasion	343	None
		0.5 mg Group		
S07441	107008	RPE Tear / Detachment	33	Dose held
S08110	117002	Hyphema	29	Meds / AC Tap
S08246	131012	Increased intraocular pressure	183	Meds / AC Tap
S06530	138002	Iridocyclitis – Recurrent	37, 119	Study drug d/ced
S08208	141005	Accidental penetration of lens with needle during injection	69	Cataract extraction
	141016	Fat embolism, retinal artery	204	Hospitalization
S08220	143017	Uveitis	62	Study drug d/ced
S08150	15306	30 letter loss of vision – Unexplained	308	Dose held
S08083	163004	Endophthalmitis	66	Meds / Surgery
S00266	167007	Incorrect route of administration	240	Dose held

Study Site ID	Subject ID	[illegible]	Day of Onset	Action Taken
S08211	170009	Round retinal hole	8	Laser
S08252	193003	30 letter loss of vision – Worsened AMD	254	None
S03675	200004	30 letter loss of vision –Vitreous hemorrhage	210	None

Table 7.1.2-2 Study FVF2587g
Serious Ocular Adverse Events in the Study Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
Verteporfin PDT Group				
S08214	321011	30 letter loss of vision – Subretinal hemorrhage	43	None
S08130	335003	30 letter loss of vision – Worsened AMD	184	None
S08222	344002	30 letter loss of vision – Unexplained	29	None
S08263	363002	30 letter loss of vision – Worsened AMD	31	None
S08255	365001	30 letter loss of vision – Worsened AMD	186, 235	None
S09325	381008	Retinal detachment	114, 189	Surgery, Study drug d/ced
0.3 mg Group				
S07441	303001	Retinal detachment	58	Surgery, Study drug d/ced
S08215	305002	30 letter loss of vision – Worsened AMD	126,169	None
S00444	319007	Vitreous hemorrhage	276	None
S08214	321006	30 letter loss of vision – Unexplained	295	None
S08325	354006	Medication Error	302	None
S08314	364002	Incorrect injection procedure – no lidocaine admin.	358	None
0.5 mg Group				
S08235	304005	Medication Error	367	None
S08146	326001	Occludable narrow angle	104	Iridotomy
S08596	334009	Corneal abrasion	29	Medication
S08211	339004	30 letter loss of vision – Submacular hemorrhage	95	Dose held, Surgery
S08248	340003	30 letter loss of vision – Worsened AMD	92	None
S08207	341003	Endophthalmitis	122	Dose held, Procedure
S08234	349006	Corneal abrasion	296	None
	349006	Afferent pupillary defect	357	Study drug and Study d/ced
S09308	389001	Recurrent uveitis	231,270	Study drug and Study d/ced

[1] Subject's vision fluctuated throughout study and was suspected of peaking at certain visits.

Reviewer's Comment:

The most frequent cause of a serious adverse event was the loss of 30 letters of vision which was usually due to progression of macular degeneration. The greatest number of these occurrences was in the sham- or Verteporfin PDT- treated groups, followed by the ranibizumab 0.3mg- and 0.5 mg-treated groups, respectively.

Table 7.1.2-3 Study FVF2598g
Serious Ocular Adverse Events in the Fellow Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
		Sham Group		
S07847	115009	30 letter loss of vision – New CNVM	306	Surgery - TPPV
		Elevated intraocular pressure – Postop	327	Medications
S08201	118004	Visual field defect – CVA	319	Hospitalization
S08239	121007	30 letter loss of vision – New CNVM	31	None
S08130	125008	30 letter loss of vision – New CNVM	50	PDT,D/C Study
S08249	136009	30 letter loss of vision – New CNVM	92	PDT
		0.3 mg Group		
S08218	114005	30 letter loss of vision – Worsened AMD	218	PDT
S07847	115002	30 letter loss of vision – Unexplained	160	None, resolved
S08248	140005	Retinal detachment	299	Surgery
		Recurrent retinal detachment	341	Surgery
S08194	176003	30 letter loss of vision – Worsened AMD	164	PDT
		0.5 mg Group		
S08216	108004	30 letter loss of vision – New CNVM	66	PDT
S07439	112004	30 letter loss of vision – Unexplained	127	None, resolved

Table 7.1.2-4 Study FVF2587g
Serious Ocular Adverse Events in the Fellow Eye during the First Treatment Year
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
		Verteporfin PDT Group		
S08314	364004	Medication Error – Nonstudy eye injected	264	None
		0.3 mg Group		
S08214	321006	30 letter loss of vision – Unexplained	337	None
S08214	321013	30 letter loss of vision – Subretinal hemorrhage	295	Laser tx
S08150	329008	30 letter loss of vision – Worsened AMD	85	PDT
S08133	358003	30 letter loss of vision – Recurrent CNVM	68	PDT, steroid injxn
S09326	390001	Sudden loss of vision - Blindness	337	PDT
		0.5 mg Group		
S08220	302013	30 letter loss of vision – Worsened AMD	246	PDT
S08214	321007	30 letter loss of vision – Worsened AMD	330	Laser, steroid injxn
S08205	342003	30 letter loss of vision [1]	234	None

[1] Patient with short term memory loss, difficult to assess vision.

Reviewer's Comment:

The most frequent cause of a serious adverse event in the fellow eye was the loss of 30 letters of vision due to progression of macular degeneration in both studies regardless of treatment group.

Table 7.1.2-5
Non-Ocular Serious Adverse Events during the First Treatment Year (Occurring in ≥ 2 Subjects in Any Group)
Safety Evaluable Subjects – Study FVF2598g and Study FVF2587g

MedDRA Preferred Terms	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3mg N=238	Ranibizumab 0.5mg N=239	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
TOTAL [a]	**39 (16.5%)**	**43 (18.1%)**	**44 (18.4%)**	**28 (19.6%)**	**20 (14.6%)**	**28 (20.0%)**
Pneumonia	4 (1.7%)	7 (2.9%)	4 (1.7%)	2 (1.4%)	4 (2.9%)	4 (2.9%)
Diverticulitis	1 (0.4%)	2 (0.8%)	3 (1.3%)	0	0	0
Syncope	4 (1.7%)	0	1 (0.8%)	0	0	0
Coronary artery disease	4 (1.7%)	0	1 (0.4%)	0	3 (2.2%)	0
Cardiac failure, congestive	3 (1.3%)	1 (0.4%)	1 (0.4%)	3 (2.1%)	0	2 (1.4%)
Chest pain	2 (0.8%)	3 (1.3%)	0	0	0	0
Cerebrovascular accident	1 (0.4%) [b]	1 (0.4%)	3 (1.3%) [c]	0	0	0
Cellulitis	3 (1.3%)	1 (0.4%)	0	0	0	0
Hip fracture	0	3 (1.3%)	1 (0.4%)	0	0	0
Asthma	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	0	0
Atrial fibrillation	2 (0.8%)	1 (0.4%)	0	1 (0.7%)	1 (0.7%)	2 (1.4%)
Lung neoplasm, malignant	2 (0.8%)	1 (0.4%)	0	0	0	0
COPD Exacerbation	1 (0.4%)	0	2 (0.8%)	2 (1.4%)	0	3 (2.1%)
COPD	0	0	0	0	0	3 (2.1%)
Abdominal pain, upper	2 (0.8%)	0	0	0	0	0
Non-cardiac chest pain	0	0	2 (0.8%)	0	0	0
Osteoarthritis	2 (0.8%)	0	0	0	0	0
Renal cell carcinoma, stage unspecified	2 (0.8%)	0	0	0	0	0
Transient ischemic attack	0	0	2 (0.8%)	0	0	0
Subdural hematoma	0	0	0	0	2 (1.5%)	0

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence. Events which occurred more frequently in the 0.5-mg group of either study are highlighted.

a Represents the number of subjects with at least one non-ocular serious adverse event. **b** The sham-treated subject (118004) who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. **c** Included one case reported as a cerebral ischemia.

Reviewer's Comment:

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus either control are highlighted. In the FVF2598g study, serious non-ocular events were evenly distributed across the ranibizumab treated groups; but, slightly less frequent in the sham treated group.

In the FVF2587g study, serious non-ocular events occurred with approximately equal frequency in the verteporfin PDT and ranibizumab 0.5 mg treated groups. The frequency was somewhat less in the ranibizumab 0.3mg- treated group.

7.1.3 Dropouts and Other Significant Adverse Events

The case report forms of all subjects who discontinued study participation were evaluated. Refer to Table 6.1.3.1-7 and Table 6.1.3.2-7 for details.

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7.1.3.1 Overall profile of dropouts

Table 7.1.3.1-1 Subject Disposition and Reasons for Discontinuation: Randomized Subjects

	Study FVF2598g Number of Subjects			Study FVF2587g Number of Subjects		
	Sham N=236	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg	Verteporfin PDT	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Randomized	238	238	240	143	140	140
Received ranibizumab or sham injection	236 (99.2%)	238 (100%)	239 (100%)	143 (100%)	137 (97.9%)	140 (100%)
Received verteporfin or sham PDT	---	---	---	143 (100%)	137 (97.9%)	140 (100%)
Completed Month 12 [a]	212 (89.1%)	226 (95.0%)	226 (94.2%)	127 (88.8%)	128 (91.4%)	131 (93.6%)
Discontinued treatment [b] prior to Month 12	31 (13.0%)	10 (4.2%)	11 (4.6%)	14 (9.8%)	13 (9.3%)	9 (6.4%)
Death	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	3 (2.1%)	2 (1.4%)
Adverse Event	6 (2.5%)	3 (1.3%)	5(2.1%)	6 (4.2%)	3 (2.1%)	4 (2.9%)
Lost to follow-up	2 (0.8%)	0	0	1 (0.7%)	0	1 (0.7%)
Subject's Decision	15 (6.3%)	6 (2.5%)	4 (1.7%)	4 (2.8%)	4 (2.9%)	2 (1.4%)
Physician's Decision	2 (0.8%)	0	1 (0.4%)	1 (0.7%)	2 (1.4%)	0
Subject non-compliance	0	0	0	0	1 (0.7%)	0
Subject's condition mandated other therapeutic intervention	6 (2.5%)	0	0	1 (0.7%)	0	0

a Defined as having a visual acuity score in the study eye at Month 12. Data from subjects who missed the Month 12 visit but stayed in the study for the second year were not counted.**b** Two subjects were discontinued from the study at Month 12 after assessments.

Reviewer's Comment:

In both studies, the sham injection and verteporfin PDT groups had higher rates of study dropout and treatment discontinuation than the ranibizumab groups.

Approximately 50% of the treatment discontinuations were due to subject decision.

7.1.3.2 Adverse events associated with dropouts

Treatment discontinuation and study dropout was most frequently associated with the subject's decision with no change in vision from baseline, subject's loss of vision and progression of age-related macular degeneration.

Table 7.1.3.2-1 Ocular Adverse Events in the Study Eye Leading to Discontinuation of Study or Treatment during the First Treatment Year: Safety Evaluable Subjects

MedDRA Preferred Terms	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=240	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
TOTAL [a]	**8 (3.4%)**	**3 (1.3%)**	**4 (1.7%)**	**1 (0.7%)**	**2 (1.5%)**	**4 (2.9%)**
Cataract subcapsular	0	0	1 (0.4%)	0	0	0
Choroidal neovascularization	4 (1.7%)	0	0	0	0	0
Conjunctivitis allergic	0	0	1 (0.4%)	0	0	0
Conjunctivitis bacterial	0	0	0	0	0	1 (0.7%)
Corneal deposits	0	0	1 (0.4%)	0	0	0
Eye pain	0	0	1 (0.4%)	0	1 (0.7%)	0
Iritis	0	2 (0.8%)	0	0	0	0
Iridocyclitis	0	0	1 (0.4%)	0	0	1 (0.7%)
Macular degeneration	3 (1.3%)	0	0	0	0	0
Ocular hyperemia	0	0	0	0	1 (0.7%)	0
Pupillary reflex impaired	0	0	0	0	0	1 (0.7%)
Retinal detachment [b]	0	0	0	1 (0.7%)	1 (0.7%)	0
Retinal hemorrhage	2 (0.8%)	1 (0.4%)	0	0	0	0
Uveitis	0	0	1 (0.4%)	0	0	1 (0.7%)
Vision blurred	0	0	0	0	1 (0.7%)	0
Vitreous detachment	2 (0.8%)	0	0	0	0	0

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence. a Represents the number of subjects with at least one ocular adverse event in the study eye that led to discontinuation of study or treatment. b Both events were rhegmatogenous retinal detachment.

Reviewer's Comment:

In Study FVF2598g, the adverse events which led to discontinuation of subjects in the sham-injection group were primarily related to progression of age-related macular degeneration. The adverse event which led to discontinuation in ranibizumab treated subjects most frequently in both studies was intraocular inflammation (iritis, iridocyclitis, and uveitis).

Ocular adverse events that led to discontinuation in the ranibizumab groups were generally those associated with intravitreal injections.

Table 7.1.3.2-2 Non-Ocular Adverse Events in the Study Eye Leading to Discontinuation of Study or Treatment during the First Treatment Year: Safety Evaluable Subjects

MedDRA Preferred Terms	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
TOTAL [a]	**5 (2.1%)**	**2 (0.8%)**	**5 (2.1%)**	**6 (4.2%)**	**5 (3.6%)**	**2 (1.4%)**
Acute myocardial infarction	0	1 (0.4%)	0	0	0	0
Asthenia	0	0	0	1 (0.7%)	1 (0.7%)	0
Asthma	0	0	1 (0.4%)	0	0	0
Blood pressure increased	1 (0.4%)	0	0	0	0	0
Cardiac arrest	0	0	0	1 (0.7%)	1 (0.7%)	0
Cardiac failure	0	0	0	0	0	1 (0.7%)
Cardiac failure chronic	0	0	0	0	0	1 (0.7%)
Cardiogenic shock	0	1 (0.4%)	0	0	0	0
Cerebral infarction	0	0	0	0	1 (0.7%)	0
Cerebral ischemia	0	0	1 (0.4%)	0	0	0
Chronic obstructive pulmonary disease exacerbated	1 (0.4%)	0	0	0	0	0
Chronic obstructive pulmonary disease	1 (0.4%)	0	0	0	0	0
Cough	0	0	1 (0.4%)	0	0	0
Gastric ulcer perforation	0	0	0	1 (0.7%)	0	0
Glioblastoma	0	0	0	1 (0.7%)	0	0
Increased upper airway secretion	0	0	1 (0.4%)	0	0	0
Intestinal infarction	0	0	1 (0.4%)	0	0	0
Lung neoplasm malignant	2 (0.8%)	0	0	0	1 (0.7%)	0
Myocardial infarction	0	0	0	1 (0.7%)	0	0
Non-Hodgkin's lymphoma	0	1 (0.4%)	0	0	0	0
Non-small cell lung cancer Stage IIIb	1 (0.7%)	0	0	0	0	0
Pelvic fracture	0	0	0	0	0	1 (0.4%)
Pneumonia	1 (0.7%)	0	0	1 (0.4%)	0	0
Respiratory arrest	0	1 (0.7%)	0	0	0	0
Viral infection	0	1 (0.7%)	0	0	0	0
Wheezing	0	0	0	0	0	1 (0.4%)

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

a Represents the number of subjects with at least one non-ocular adverse event in the study eye that led to discontinuation of study or treatment.

Reviewer's Comment:
No pattern of non-ocular adverse events leading to study or treatment discontinuation was noted in either study. The non-ocular adverse events reported were conditions commonly seen in an elderly population.

7.1.3.3 Other significant adverse events

Table 7.1.3.3-1 Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year: Studies FVF2598g and FVF2587g

Type of Adverse Event	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239	Verteporfin PDT N=143	Ranibizumab 0.5 mg N=[illegible]	Ranibizumab 0.5 mg N=140
TOTAL [a]	**2 (0.8%)**	**8 (3.4%)**	**9 (3.8%)**	**3 (2.1%)**	**4 (2.9%)**	**8 (5.7%)**
Hypertension events	0	1 (0.4%)	0	0	0	0
Arterial thromboembolic events	2 (0.8%)	5 (2.1%)	8 (3.3%)	2 (1.4%)	2 (1.4%)	4 (2.9%)
Non-ocular hemorrhages	0	1 (0.4%)	0	0	2 (1.5%)	3 (2.1%)
Other potentially associated events	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

Reviewer's Comment:
In the two phase 3 studies, a small trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition was noted at Month 12, particularly in the ranibizumab 0.5-mg dose group. This reflects trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria). No imbalance in overall adverse events potentially related to systemic VEGF inhibition was observed among treatment groups.

Differing definitions, assessment methods, and reporting of arterial thromboembolic events makes there analysis challenging. The sponsor applied the Antiplatelet Trialists' Collaboration (APTC) classification (Antiplatelet Trialists' Collaborations 1994) to the adverse events which mitigates some of these issues by focusing on a more restricted but well-defined spectrum of serious adverse events: vascular deaths (including deaths of unknown cause), nonfatal myocardial infarction, nonfatal ischemic stroke, and nonfatal hemorrhagic stroke.

Table 7.1.3.3-2 APTC Arterial Thromboembolic Events during the First Treatment Year: Studies FVF2598g and FVF2587g

Type of Adverse Event	Study FVF2598g			Study FVF2587g			Pooled
	Sham	Ranibizumab		Verteporfin PDT	Ranibizumab		Ranibizumab
	N=236	0.3 mg N=238	0.5 mg N=239	N=143	0.3 mg N=137	0.5 mg N=140	0.5 mg N=379
TOTAL [a]	**2 (0.8%)**	**3 (1.3%)**	**5 (2.1%)**	**3 (2.1%)**	**3 (2.2%)**	**6 (4.3%)**	**11 (2.9%)**
Vascular deaths	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	3 (0.8%)
Nonfatal myocardial infarction	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	3 (2.1%)	4 (1.1%)
Nonfatal ischemic stroke	1 (0.4%)	1 (0.4%)	3 (1.3%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	4 (1.1%)
Nonfatal hemorrhagic stroke	0	0	0	0	0	0	0

Note: Arterial thromboembolic events, defined according to the Antiplatelet Trialists' Collaboration classification (1994), are presented.

Reviewer's Comment:

Applying the APTC classification to the serious adverse events, an overall trend is noted in the ranibizumab 0.5-mg dose group compared to subjects in other treatment groups. The overall frequency of such events in the ranibizumab 0.3-mg group was 6 events in 375 subjects (1.6%), 5 events in 379 subjects (1.3%) for the control groups. The overall frequency of such events in the 0.5-mg ranibizumab groups was 11 events in 379 subjects (2.9%).

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Table 7.1.3.3-3 Intraocular Inflammation in the Study Eye during the First Treatment Year Studies FVF2598g and FVF2587g: Safety Evaluable Subjects

MedDRA Preferred Terms	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
TOTAL [a]	**23 (9.7%)**	**26 (10.9%)**	**34 (14.2%)**	**4 (2.8%)**	**14 (10.2%)**	**21 (15.0%)**
Iritis	16 (6.8%)	15 (6.3%)	15 (6.3%)	2 (1.4%)	7 (5.1%)	10 (7.1%)
Vitritis	7 (3.0%)	13 (5.5%)	22 (9.2%)	2 (1.4%)	8 (5.8%)	12 (8.6%)
Iridocyclitis	2 (0.8%)	1 (0.4%)	2 (0.8%)	0	0	4 (2.9%)
Uveitis	2 (0.8%)	0	1 (0.4%)	0	0	1 (0.7%)

Reviewer's Comment:
There was a dose dependent relationship between ranibizumab and intraocular inflammation in both studies.

In Study FVF2598g, four ranibizumab subjects had serious intraocular inflammation, two subjects in each treatment group. Two of those subjects discontinued treatment as a result. One case of serious uveitis (0.5-mg group) was treated with intravitreal antibiotics.

In Study FVF2587g, one subject in the ranibizumab 0.5 mg groups experienced a case of uveitis deemed serious. The first episode in this subject was treated with antibiotics. The second occurrence led to treatment discontinuation.

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7.1.4 Other Search Strategies

No other search strategies were used to analyze adverse events.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The protocol adequately defined an adverse event. Each investigator evaluated study participants for adverse events, volunteered and elicited, at each intraocular-pressure check on each study visit. An Adverse Event Form was completed to document a description of the event, onset, severity, treatment required, outcome and relatedness to the use of the study medication. Checklists were not used.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The study utilized the MedDRA preferred terms for adverse event recording. The terms were sufficiently descriptive to assess adverse events expected to be experienced by the study population.

7.1.5.3 Incidence of common adverse events

Table 7.1.5.3-1

Adverse Events Occurring in ≥ 1 % of Patients during the First Treatment Year: Pooled Safety Evaluable Subjects – Study FVF2598g and Study FVF2587g

MedDRA System Organ Class Preferred Term	Sham N=236	Verteporfin PDT N=143	Ranibizumab Pooled 0.3 mg N=375	 0.5 mg N=379
Blood and Lymphatic System Disorders				
Anemia	8 (3.4%)	4 (2.8%)	11 (2.9%)	17 (4.5%)
Thrombocytopenia	0	0	3 (0.8%)	0
Cardiac Disorders				
Atrial fibrillation	5 (2.1%)	3 (2.1%)	6 (1.6%)	7 (1.8%)
Cardiac failure congestive	4 (1.7%)	4 (2.8%)	3 (0.8%)	5 (1.3%)
Coronary artery disease	5 (2.1%)	0	3 (0.8%)	4 (1.1%)
Ear and Labyrinth Disorders				
Vertigo	2 (0.8%)	5 (3.5%)	7 (1.9%)	3 (0.8%)
Endocrine Disorders				
Hypothyroidism	2 (0.8%)	2 (1.4%)	3 (0.8%)	0
Eye Disorders				
Abnormal sensation in eye	4 (1.7%)	0	6 (1.6%)	1 (0.3%)
Altered visual depth perception	3 (1.3%)	0	0	0
Anterior chamber flare	6 (2.5%)	0	7 (1.9%)	7 (1.8%)
Arcus lipoides	0	0	6 (1.6%)	7 (1.8%)
Blepharitis	14 (5.9%)	6 (4.2%)	22 (5.9%)	33 (8.7%)
Cataract	26 (11.0%)	10 (7.0%)	37 (9.9%)	43 (11.3%)
Choroidal neovascularization	27 (11.4%)	14 (9.8%)	4 (1.1%)	8 (2.1%)
Conjunctival hemorrhage	139 (58.9%)	65 (45.5%)	261 (69.6%)	255 (67.3%)
Conjunctival hyperemia	14 (5.9%)	5 (3.5%)	19 (5.1%)	22 (5.8%)
Conjunctival edema	3 (1.3%)	2 (1.4%)	4 (1.1%)	2 (0.5%)
Conjunctivitis	7 (3.0%)	0	7 (1.9%)	7 (1.8%)
Conjunctivitis, allergic	3 (1.3%)	1 (0.7%)	3 (0.8%)	9 (2.4%)
Corneal abrasion	7 (3.0%)	0	6 (1.6%)	11 (2.9%)

MedDRA System Organ Class Preferred Term	[redacted]	[redacted]	Ranibizumab Pooled 0.5 mg N=475	Ranibizumab Pooled 0.5 mg N=379
Corneal dystrophy	2 (0.8%)	0	17 (4.5%)	13 (3.4%)
Cutis laxa	1 (0.4%)	0	4 (1.1%)	3 (0.8%)
Detachment of retinal pigment epithelium	30 (12.7%)	5 (3.5%)	26 (6.9%)	22 (5.8%)
Drug hypersensitivity	4 (1.7%)	6 (4.2%)	1 (0.3%)	3 (0.8%)
Dry Eye	12 (5.1%)	12 (8.4%)	15 (4.0%)	30 (7.9%)
Eye discharge	14 (5.9%)	4 (2.8%)	20 (5.3%)	13 (3.4%)
Eye hemorrhage	7 (3.0%)	0	2 (0.5%)	3 (0.8%)
Eye irritation	43 (18.2%)	8 (5.6%)	40 (10.7%)	40 (10.6%)
Eye pain	57 (24.2%)	24 (16.8%)	110 (29.3%)	105 (27.7%)
Eye pruritus	20 (8.5%)	7 (4.9%)	28 (7.5%)	29 (7.7%)
Eye swelling	4 (1.7%)	2 (1.4%)	3 (0.8%)	4 (1.1%)
Eyelid margin crusting	1 (0.4%)	0	6 (1.6%)	1 (0.3%)
Eyelid edema	4 (1.7%)	2 (1.4%)	10 (2.7%)	9 (2.4%)
Eyelid pain	1 (0.4%)	0	3 (0.8%)	6 (1.6%)
Eyelid ptosis	3 (1.3%)	0	4 (1.1%)	2 (0.5%)
Eyelids pruritis	4 (1.7%)	1 (0.7%)	2 (0.5%)	2 (0.5%)
Foreign body sensation in eyes	27 (11.4%)	15 (10.5%)	49 (13.1%)	49 (12.9%)
Glaucoma	0	2 (1.4%)	2 (0.5%)	2 (0.5%)
Injection site hemorrhage	3 (1.3%)	3 (2.1%)	8 (2.1%)	13 (3.4%)
Intraocular pressure increased	7 (3.0%)	10 (7.0%)	59 (15.7%)	61 (16.1%)
Iridocyclitis	0	0	0	4 (1.1%)
Iritis	16 (6.8%)	2 (1.4%)	22 (5.9%)	25 (6.6%)
Lacrimation increased	30 (12.7%)	6 (4.2%)	41 (10.9%)	35 (9.2%)
Macular degeneration	125 (53.0%)	89 (62.2%)	138 (36.8%)	136 (35.9%)
Macular edema	20 (8.5%)	6 (4.2%)	4 (1.1%)	10 (2.6%)
Macular scar	2 (0.8%)	1 (0.7%)	6 (1.6%)	5 (1.3%)
Maculopathy	19 (8.1%)	5 (3.5%)	15 (4.0%)	26 (6.9%)
Migraine with aura	0	2 (1.4%)	0	0
Ocular discomfort	7 (3.0%)	1 (0.7%)	20 (5.3%)	19 (5.0%)
Ocular hyperemia	16 (6.8%)	1 (0.7%)	23 (6.1%)	26 (6.9%)
Optic disc hemorrhage	3 (1.3%)	0	0	0
Optic nerve C/D ratio increased	0	2 (1.4%)	0	1 (0.3%)
Photophobia	6 (2.5%)	2 (1.4%)	6 (1.6%)	9 (2.4%)
Photopsia	13 (5.5%)	8 (5.6%)	14 (3.7%)	11 (2.9%)
Posterior capsule opacification	7 (3.0%)	2 (1.4%)	11 (2.9%)	9 (2.4%)
Punctate keratitis	6 (2.5%)	2 (1.4%)	9 (2.4%)	6 (1.6%)
Retinal degeneration	11 (4.7%)	2 (1.4%)	21 (5.6%)	23 (6.1%)
Retinal detachment	12 (5.1%)	2 (1.4%)	15 (4.0%)	8 (2.1%)
Retinal disorder	15 (6.4%)	2 (1.4%)	28 (7.5%)	33 (8.7%)
Retinal exudates	18 (7.6%)	5 (3.5%)	20 (5.3%)	17 (4.5%)
Retinal hemorrhage	101 (42.8%)	76 (53.1%)	66 (17.6%)	66 (17.4%)
Retinal edema	4 (1.7%)	0	5 (1.3%)	1 (0.3%)
Retinal pigmentation	1 (0.4%)	0	5 (1.3%)	3 (0.8%)
Retinal scar	3 (1.3%)	3 (2.1%)	5 (1.3%)	3 (0.8%)
Retinal vascular disorder	7 (3.0%)	1 (0.7%)	0	6 (1.6%)
Scleral hyperemia	3 (1.3%)	0	1 (0.3%)	1 (0.3%)
Sebaceous gland disorder	0	0	1 (0.3%)	4 (1.1%)
Subretinal fibrosis	24 (10.2%)	27 (18.9%)	33 (8.8%)	28 (7.4%)
Vision blurred	15 (6.4%)	9 (6.3%)	27 (7.2%)	24 (9.0%)

MedDRA System Organ Class Preferred Term	[redacted]	[redacted]	Ranibizumab Pooled	
	[redacted]	[redacted]	0.3 mg N=375	0.5 mg N=379
Visual acuity reduced	23 (9.7%)	21 (14.7%)	25 (6.7%)	21 (5.5%)
Visual disturbance	14 (5.9%)	6 (4.2%)	30 (8.0%)	30 (7.9%)
Vitreous degeneration	3 (1.3%)	0	2 (0.5%)	0
Vitreous detachment	30 (12.7%)	26 (18.2%)	60 (16.0%)	59 (15.6%)
Vitreous disorder	0	0	4 (1.1%)	1 (0.3%)
Vitreous floaters	14 (5.9%)	6 (4.2%)	75 (20.0%)	78 (20.6%)
Vitreous hemorrhage	3 (1.3%)	3 (2.1%)	8 (2.1%)	8 (2.1%)
Vitritis	7 (3.0%)	2 (1.4%)	21 (5.6%)	34 (9.0%)
Gastrointestinal Disorders				
Abdominal discomfort	1 (0.4%)	0	1 (0.3%)	4 (1.1%)
Abdominal pain upper	4 (1.7%)	3 (2.1%)	0	1 (0.3%)
Colonic polyp	3 (1.3%)	1 (0.7%)	3 (0.8%)	4 (1.1%)
Constipation	0	3 (2.1%)	4 (1.1%)	4 (1.1%)
Diarrhea	12 (5.1%)	6 (4.2%)	16 (4.3%)	9 (2.4%)
Diverticulum intestinal	0	2 (1.4%)	0	0
Dyspepsia	7 (3.0%)	3 (2.1%)	5 (1.3%)	3 (0.8%)
Gastroesophageal reflux disease	6 (2.5%)	8 (5.6%)	10 (2.7%)	11 (2.9%)
Hemorrhoids	4 (1.7%)	1 (0.7%)	1 (0.3%)	4 (1.1%)
Hiatus hernia	0	2 (1.4%)	0	3 (0.8%)
Nausea	10 (4.2%)	7 (4.9%)	20 (5.3%)	19 (5.0%)
Stomach discomfort	0	3 (2.1%)	0	0
Toothache	4 (1.7%)	2 (1.4%)	3 (0.8%)	3 (0.8%)
Vomiting	2 (0.8%)	6 (4.2%)	6 (1.6%)	3 (0.8%)
General Disorders and Administration Site Conditions				
Asthenia	4 (1.7%)	3 (2.1%)	3 (0.8%)	5 (1.3%)
Chest pain	7 (3.0%)	0	7 (1.9%)	4 (1.1%)
Fatigue	4 (1.7%)	2 (1.4%)	6 (1.6%)	4 (1.1%)
Edema peripheral	9 (3.8%)	0	9 (2.4%)	7 (1.8%)
Pain	2 (0.8%)	0	4 (1.1%)	3 (0.8%)
Pyrexia	2 (0.8%)	2 (1.4%)	9 (2.4%)	5 (1.3%)
Immune System Disorders				
Drug hypersensitivity	3 (1.3%)	1 (0.7%)	4 (1.1%)	5 (1.3%)
Hypersensitivity	1 (0.4%)	3 (2.1%)	6 (1.6%)	6 (1.6%)
Seasonal allergy	2 (0.8%)	6 (4.2%)	7 (1.9%)	7 (1.8%)
Infections and Infestations				
Bronchitis	12 (5.1%)	9 (6.3%)	20 (5.3%)	23 (6.1%)
Bronchitis, chronic	0	2 (1.4%)	0	0
Cellulitis	3 (1.3%)	0	5 (1.3%)	3 (0.8%)
Cystitis	1 (0.4%)	2 (1.4%)	6 (1.6%)	8 (2.1%)
Diverticulitis	2 (0.8%)	0	7 (1.9%)	7 (1.8%)
Ear infection	2 (0.8%)	3 (2.1%)	4 (1.1%)	4 (1.1%)
Fungal infection	1 (0.4%)	0	1 (0.3%)	4 (1.1%)
Gastroenteritis, viral	5 (2.1%)	0	6 (1.6%)	11 (2.9%)
Herpes zoster	3 (1.3%)	0	10 (2.7%)	5 (1.3%)
Influenza	6 (2.5%)	1 (0.7%)	13 (3.5%)	14 (3.7%)
Kidney infection	4 (1.7%)	0	3 (0.8%)	2 (0.5%)
Localised infection	5 (2.1%)	0	3 (0.8%)	4 (1.1%)
Nasopharyngitis	23 (9.7%)	15 (10.5%)	42 (11.2%)	22 (5.8%)
Pneumonia	10 (4.2%)	5 (3.5%)	15 (4.0%)	13 (3.4%)

MedDRA System Organ Class Preferred Term			Ranibizumab Pooled 0.5 mg N=375	 0.5 mg N=379
Sinusitis	9 (3.8%)	9 (6.3%)	20 (5.3%)	21 (5.5%)
Skin infection	3 (1.3%)	0	0	1 (0.3%)
Tooth abscess	3 (1.3%)	0	2 (0.5%)	2 (0.5%)
Tooth infection	0	0	4 (1.1%)	3 (0.8%)
Upper respiratory tract infection	15 (6.4%)	6 (4.2%)	23 (6.1%)	19 (5.0%)
Urinary tract infection	12 (5.1%)	9 (6.3%)	21 (5.6%)	18 (4.7%)
Injury, Poisoning and Procedural Complications Contrast Media Reaction				
Contusion	6 (2.5%)	5 (3.5%)	8 (2.1%)	7 (1.8%)
Excoriation	2 (0.8%)	1 (0.7%)	5 (1.3%)	5 (1.3%)
Fall	5 (2.1%)	1 (0.7%)	7 (1.9%)	8 (2.1%)
Hip fracture	0	0	4 (1.1%)	1 (0.3%)
Muscle strain	6 (2.5%)	0	4 (1.1%)	1 (0.3%)
Post procedural pain	3 (1.3%)	1 (0.7%)	1 (0.3%)	2 (0.5%)
Skin laceration	3 (1.3%)	2 (1.4%)	9 (2.4%)	4 (1.1%)
Tooth injury	0	2 (1.4%)	2 (0.5%)	0
Wrist fracture	3 (1.3%)	0	3 (0.8%)	2 (0.5%)
Investigations				
Blood cholesterol increased	4 (1.7%)	2 (1.4%)	2 (0.5%)	7 (1.8%)
Blood glucose increased	4 (1.7%)	3 (2.1%)	9 (2.4%)	8 (2.1%)
Blood pressure increased	14 (5.9%)	3 (2.1%)	18 (4.8%)	17 (4.5%)
Heart rate irregular	0	2 (1.4%)	1 (0.3%)	0
Prostate specific antigen increased	2 (0.8%)	2 (1.4%)	4 (1.1%)	4 (1.1%)
Weight decreased	3 (1.3%)	2 (1.4%)	2 (0.5%)	0
Metabolism and Nutrition Disorders				
Dehydration	0	2 (1.4%)	3 (0.8%)	1 (0.3%)
Diabetes mellitus	0	1 (0.7%)	4 (1.1%)	9 (2.4%)
Gout	3 (1.3%)	1 (0.7%)	4 (1.1%)	8 (2.1%)
Hypercholoesterolemia	5 (2.1%)	4 (2.8%)	7 (1.9%)	9 (2.4%)
Hyperlipidemia	1 (0.4%)	2 (1.4%)	4 (1.1%)	5 (1.3%)
Hypokalemia	4 (1.7%)	3 (2.1%)	7 (1.9%)	2 (0.5%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	14 (5.9%)	9 (6.3%)	19 (5.1%)	18 (4.7%)
Arthritis	14 (5.9%)	5 (3.5%)	9 (2.4%)	12 (3.2%)
Back pain	13 (5.5%)	13 (9.1%)	22 (5.9%)	15 (4.0%)
Bone pain	0	3 (2.1%)	0	0
Bursitis	6 (2.5%)	0	1 (0.3%)	1 (0.3%)
Exostosis	0	2 (1.4%)	0	1 (0.3%)
Joint swelling	4 (1.7%)	0	3 (0.8%)	1 (0.3%)
Muscle spasms	3 (1.3%)	3 (2.1%)	6 (1.6%)	5 (1.3%)
Myalgia	0	2 (1.4%)	0	0
Neck pain	1 (0.4%)	0	4 (1.1%)	5 (1.3%)
Osteoarthritis	5 (2.1%)	0	4 (1.1%)	1 (0.3%)
Osteoporosis	0	5 (3.5%)	1 (0.3%)	4 (1.1%)
Pain in extremity	7 (3.0%)	4 (2.8%)	13 (3.5%)	10 (2.6%)
Rotator cuff syndrome	3 (1.3%)	0	0	3 (0.8%)
Shoulder pain	7 (3.0%)	1 (0.7%)	6 (1.6%)	4 (1.1%)
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)				
Basal cell carcinoma	8 (3.4%)	2 (1.4%)	10 (2.7%)	6 (1.6%)
Seborrheic keratosis	0	2 (1.4%)	1 (0.3%)	1 (0.3%)

MedDRA System Organ Class Preferred Term	[redacted]	[redacted]	Ranibizumab Pooled 0.3 mg N=375	Ranibizumab Pooled 0.5 mg N=379
Skin cancer	1 (0.4%)	0	4 (1.1%)	3 (0.8%)
Skin papilloma	0	2 (1.4%)	1 (0.3%)	1 (0.3%)
Nervous System Disorders				
Dizziness	16 (6.8%)	4 (2.8%)	14 (3.7%)	12 (3.2%)
Headache	15 (6.4%)	7 (4.9%)	35 (9.3%)	25 (6.6%)
Syncope	4 (1.7%)	3 (2.1%)	2 (0.5%)	6 (1.6%)
Transient ischemic attack	0	2 (1.4%)	0	2 (0.5%)
Psychiatric Disorders				
Anxiety	1 (0.4%)	8 (5.6%)	11 (2.9%)	11 (2.9%)
Depression	8 (3.4%)	7 (4.9%)	9 (2.4%)	12 (3.2%)
Insomnia	7 (3.0%)	2 (1.4%)	8 (2.1%)	14 (3.7%)
Renal and Urinary Disorders				
Nephrolithiasis	0	3 (2.1%)	3 (0.5%)	0
Renal cyst	0	3 (2.1%)	1 (0.3%)	0
Reproductive System and Breast Disorders				
Benign prostatic hyperplasia	1 (0.4%)	2 (1.4%)	3 (0.8%)	8 (2.1%)
Prostatitis	0	2 (1.4%)	0	1 (0.3%)
Respiratory, Thoracic and Mediastinal Disorders				
Asthma	2 (0.8%)	3 (2.1%)	8 (2.1%)	7 (1.8%)
Chronic obstructive airways disease, exacerbated	1 (0.4%)	2 (1.4%)	0	11 (2.9%)
Chronic obstructive pulmonary disease	0	1 (0.7%)	3 (0.8%)	4 (1.1%)
Cough	10 (4.2%)	8 (5.6%)	32 (8.5%)	20 (5.3%)
Dyspnea	3 (1.3%)	4 (2.8%)	10 (2.7%)	8 (2.1%)
Emphysema	0	3 (2.1%)	1 (0.3%)	2 (0.5%)
Epistaxis	0	2 (1.4%)	2 (0.5%)	1 (0.3%)
Hypoxia	3 (1.3%)	0	2 (0.5%)	0
Pharyngolarygeal pain	1 (0.4%)	4 (2.8%)	3 (0.8%)	3 (0.8%)
Rhinitis allergic	0	2 (1.4%)	0	0
Rhinorrhea	3 (1.3%)	1 (0.7%)	7 (1.9%)	4 (1.1%)
Sinus congestion	3 (1.3%)	0	5 (1.3%)	2 (0.5%)
Skin and Subcutaneous Disorders				
Actinic keratosis	6 (2.5%)	1 (0.7%)	4 (1.1%)	1 (0.3%)
Decubitus ulcer	0	2 (1.4%)	0	0
Pruritus	2 (0.8%)	1 (0.7%)	4 (1.1%)	8 (2.1%)
Rash	9 (3.8%)	4 (2.8%)	9 (2.4%)	8 (2.1%)
Surgical and Medical Procedures				
Nasal sinus drainage	0	0	0	5 (1.3%)
Vascular Disorders				
Hypertension	23 (9.7%)	12 (8.4%)	23 (6.1%)	29 (7.7%)
Hypotension	4 (1.7%)	3 (2.1%)	3 (0.8%)	0
Orthostatic hypotension	0	2 (1.4%)	0	0

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

Reviewer's Comment:

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus either control are highlighted.

Adverse events which occurred most frequently (i.e.≥ 10%) in the study eye of the ranibizumab treatment groups were conjunctival hemorrhage, eye pain, increased IOP, retinal disorder, and vitreous floaters. Many of these adverse events are commonly associated with conjunctival anesthetic and intravitreal injection procedures.

Elevated intraocular pressure was seen in a higher percentage of subjects in the ranibizumab groups than the sham-injection group. The ranibizumab subjects were also found to use ocular hypotensive and antihypertensive agents more frequently. This trend with the use of antihypertensive agents was noted at screening as well.

Intraocular inflammation including the Med DRA preferred terms iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation was experienced at an increased rate in ranibizumab treated subjects in both studies. In study FVF2598g, 60 of 477 subjects (12.5%) and in study FVF2587g 35 of 277 subjects (12.6%) in the ranibizumab groups experienced intraocular inflammation in the study eye. Findings from the objective slit lamp examination were consistent with occurrence of intraocular inflammation adverse events and are discussed

Table 7.1.5.3-2 Ocular Adverse Events in the Fellow Eye during the First Treatment Year Occurring in ≥ 5 % of Patients: Safety Evaluable Population

MedDRA System Preferred Term	Sham N=236	Verteporfin PDT N=143	Ranibizumab Pooled 0.3 mg N=375	Ranibizumab Pooled 0.5 mg N=379
Total [a]	**168 (71.2%)**	**104 (72.7%)**	**258 (68.8%)**	**265 (69.9%)**
Macular degeneration	60 (25.4%)	32 (22.4%)	91 (24.3%)	83 (21.9%)
Retinal hemorrhage	47 (19.9%)	26 (18.2%)	68 (18.1%)	71 (18.7%)
Vitreous detachment	31 (13.1%)	17 (11.9%)	43 (11.5%)	39 (10.3%)
Blepharitis	16 (6.8%)	6 (4.2%)	25 (6.6%)	29 (7.7%)
Cataract	10 (4.2%)	5 (3.5%)	16 (4.3%)	19 (5.0%)
Choroidal neovascularization	11 (4.7%)	6 (4.2%)	28 (7.5%)	29 (7.7%)
Dry Eye	13 (5.5%)	12 (8.4%)	12 (3.2%)	19 (5.0%)
Retinal disorder	11 (4.7%)	2 (1.4%)	17 (4.5%)	21 (5.5%)
Visual acuity reduced	18 (7.6%)	9 (6.3%)	13 (3.5%)	15 (4.0%)

Reviewer's Comment:
Ocular adverse events seen in the fellow eye during the first treatment year are those expected in this patient population.

7.1.5.4 Common adverse event tables
Refer to Section 7.1.5.3 Incidence of Common Adverse Events

7.1.5.5 Identifying common and drug-related adverse events

Reviewer's Comment:
Intraocular inflammation which includes Med DRA preferred terms iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation was noted to occur in a dose dependent manner in the ranibizumab treated subjects in both studies. In study FVF2598g, 60 of 477 subjects (12.5%) and in study FVF2587g 35 of 277 subjects (12.6%) in the ranibizumab groups experienced intraocular inflammation in the study eye. Findings from the objective slit lamp examination were consistent with occurrence of intraocular inflammation adverse events.

Refer to Table 7.1.3.3-3 Intraocular Inflammation in the Study Eye during the First Treatment Year Studies FVF2598g and FVF2587g: Safety Evaluable Subjects for details.

7.1.5.6 Additional analyses and explorations
Not applicable. There were no additional analyses or explorations performed regarding adverse events.

7.1.6 Less Common Adverse Events
The overall safety population was not sufficiently large to identify rare events of significant concern.

7.1.7 Laboratory Findings
During clinical trials FVF2587g and FVF2598g, laboratory assessments were to be performed on all of the subjects at the Screening Visit and Month 12 or Early Termination Visit.

Reviewer's Comment:
None of the laboratory abnormalities noted were serious adverse events, led to treatment or study discontinuation.

7.1.7.1 Overview of laboratory testing in the development program
Laboratory testing during the development program was performed to determine systemic ranibizumab concentrations, immunoreactivity to ranibizumab and if any significant changes in blood chemistry, hematology or coagulation measures could be found.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values
Such analyses were not performed. Laboratory investigations were limited by the low to non-detectable ranibizumab concentrations after intravitreal injection.

7.1.7.3 Standard analyses and explorations of laboratory data
The analyses of laboratory data consisted of description of the findings.

7.1.7.4 Additional analyses and explorations
No additional analyses and explorations were performed.

7.1.7.5 Special assessments
Laboratory abnormality adverse events were reported in less than 2% of subjects. None of the laboratory abnormalities were serious adverse events, led to treatment or study discontinuation or were considered by the investigators as study drug related.

7.1.8 Vital Signs

Vital signs were measured at the Screening Visit and at each monthly visit post treatment. Overall, on average, both ranibizumab-treated and sham-treated subjects showed little change from baseline in vital signs throughout the first treatment year. There were no meaningful between group differences in the mean change from baseline in the temperature, pulse rate and respiration rate.

Regarding blood pressure, at Month 12, the mean changes from baseline were -1.6, -0.6, and -4.4 mmHg in systolic pressure and -2.0, -1.7, and -0.5 mm Hg in diastolic pressure for the sham, 0.3-mg, and 0.5-mg groups, respectively.

Some subjects had adverse events of increased blood pressure, worsening of preexisting hypertension, or newly diagnosed hypertension during the first treatment year. There was no imbalance among treatment groups in the proportion of subjects with such adverse events (15.7% in the sham group, 13.4% in the 0.3-mg group, and 12.6% in the 0.5-mg group.)

7.1.8.1 Overview of vital signs testing in the development program
Refer to Section 7.1.1.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons
These analyses were not performed.

7.1.8.3 Standard analyses and explorations of vital signs data
These analyses were not performed.

7.1.8.4 Additional analyses and explorations
Additional analyses and explorations of vital signs data were not performed.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not obtained during the development program for this product.

7.1.10 Immunogenicity

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies.

There was no imbalance between ranibizumab-treated and sham-treated subjects regarding immunoreactivity to ranibizumab. The assay indicated positivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. All three treatment groups had similar increases in positivity during the treatment period.

Table 7.1.10-1 Immunoreactivity to Ranibizumab in the First Treatment Year

Visit	Study FVF2598g			Study FVF2587g		
	Sham	Ranibizumab		Verteporfin PDT	Ranibizumab	
	N=236	0.3 mg N=238	0.5 mg N=240	N=143	0.3 mg N=137	0.5 mg N=140
Screening	5/215 (2.3%)	6/215 (2.8%)	7/218 (3.2%)	8/131 (6.1%)	12/125 (9.6%)	7/123 (5.7%)
Month 6	19/201 (9.5%)	15/211 (7.1%)	17/207 (8.2%)	6/114 (5.3%)	11/120 (9.2%)	10/116 (8.6%)
Month 12	20/206 (9.7%)	22/222 (9.9%)	26/219 (11.9%)	7/125 (5.6%)	9/123 (7.3%)	16/129 (12.4%)

Note: Table entries are numbers of subjects with positive immunoreactivity over numbers of subjects with evaluable samples. LTR=0.7 log titer.

Exploratory subgroup analyses based on immunoreactivity to ranibizumab were performed to determine whether the appearance of immunoreactivity was related to key safety and efficacy outcomes. The analysis population was divided into three subgroups: subjects who had a negative or missing test result at screening and negative post-baseline results, subjects who had a negative or missing test result at screening but at least one positive post-baseline result, and subjects who had a positive test result at screening. Visual acuity outcomes and the occurrence of intraocular inflammation and autoimmune adverse events were examined by treatment group for each immunoreactivity subgroup. No clinically relevant differences between immunoreactivity subgroups were identified in study FVF2598g.

In Study FVF2587g, with regard to intraocular inflammation adverse events, proportionately more ranibizumab-treated subjects who were immunoreactive at some time point experienced intraocular inflammation events than subjects who were never immunoreactive. Twenty- eight percent (5 of 18) of ranibizumab-treated subjects who were immunoreactive during treatment only and thirty-two percent of subjects (6 of 19) who were immunoreactive at baseline experienced inflammation adverse events in the study eye, compared with 10% of ranibizumab-treated subjects (23 of 230) who were never immunoreactive. Of the 12 verteporfin PDT-treated subjects who were immunoreactive at some time point, none experienced an intraocular inflammation adverse event.

Table 7.1.10-2 Intraocular Inflammation in Subjects with Immunoreactivity Based on the Initial and Confirmatory Assays (ECLAs 4.FBV.8 and 4.FBV.10) Studies FVF2428g, FVF2587g, FVF3192g (First Treatment Year) and FVF2598g (2-Year Treatment Period) Safety Evaluable Subjects

Study	Treatment Group	Subject ID	Study Day / Visit of Positive Immunoreactivity Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
FVF2428g [1]	Verteporfin PDT + sham	91103	34 / Month 1	1.200	Iritis	Month 4
	Verteporfin PDT + Ranibizumab 0.5 mg	91308	- 7 / Screening	0.884	No	
			366 / Month 12	0.767		
FVF2587g	Verteporfin PDT	319001	386 / Month 12	0.797	No	---
		334008	-12 / Screening	1.130	No	
			190 / Month 6	0.902	No	
		401002	-8 / Screening	1.820	No	
			186 / Month 6	1.780		
			361 / Month 12	1.800		
	Ranibizumab 0.3mg	321003	-7 / Screening	0.945	Yes – Vitritis	Screen.,Month 1
		334003	176 / Month 6	2.300	Yes – Iritis	Month 4 [2]
		337012	-26 / Screening	0.938	Yes – Iritis	Month 5 [3]
		351004	344 / Month 12	2.190	No	---
		352006	-10 / Screening	2.070	No	---
			180 / Month 6	1.890	No	---
			362 / Month 12	1.860	No	---
		403003	-1 / Screening	0.910	No	---
	Ranibizumab 0.5mg	306020	174 / Month 6	1.530	Yes – Vitritis	Months 1 and 2
			362 / Month 12	1.850		
		337009	364 / Month 12	1.270	No	---
		342007	174 / Month 6	2.450	Yes – Iritis, Vitritis	Month 11 [4]
			360 / Month 12	3.060		
		346001	182 / Month 6	1.260	No	---

Study	Treatment Group	Subject ID	Study Day / Visit of Positive Immunoreactivity Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
			361 / Month 12	1.770		
		389001	-28 / Screening	1.240		
			182 / Month 6	0.993	Yes – Uveitis [5]	Month 7
			365 / Month 12	0.952		
FVF2598g	**Sham**	102008	183 / Month 6	1.230	No	---
			358 / Month 12	2.090		
			463 / Early term.	2.060		
		116002	723 / Month 24	2.560	No	
		139004	-28 / Screening	2.100	Yes – Iritis	Day 7
			176 / Month 6	2.060		
			358 / Month 12	2.170		
			729 / Month 24	2.340		
		150005	181 / Month 6	0.864	No	---
			393 / Month 12	0.863		
		182003	355 / Month 12	0.903	No	---
	Ranibizumab 0.3mg	101021	361 / Month 12	1.850	No	
			719 / Month 24	1.810		
		110004	728 / Month 24	1.490	No	---
		112002	716 / Month 24	0.866	No	---
		125007	183 / Month 6	0.918	No	---
		141009	721 / Month 24	1.270	No	
		143001	-13 / Screening	3.550	Iritis	Month 2
			177 / Month 6	3.740		
		146001	714 / Month 24	1.080	No	
		149006	364 / Month 12	3.150	Iritis	Month 15 [6]
			717 / Month 24	2.120		
		159013	360 / Month 12	2.000	No	
			724 / Month 24	1.890		
		165002	-21 / Screening	0.910	No	
			175 / Month 6	0.993		
			368 / Month 24	0.793		

Study	Treatment Group	Subject ID	Study Day / Visit of Positive Immunoreactivity Assay	Immunoreactivity Assay Log Titer	Any Intraocular Inflammation Diagnosis	Study Visit of Intraocular Inflammation Diagnosis
		170010	365 / Month 12	2.770	No	
			715 / Month 24	2.800		
		177006	358 / Month 12	1.870	Iritis	Day 7
			717 / Month 24	1.850		
	Ranibizumab 0.5 mg	102001	722 / Month 24	0.922	No	
		104002	719 / Month 24	1.140	No	
		106002	722 / Month 24	1.130	No	
		122002	359 / Month 12	1.630	No	
			723 / Month 24	1.770		
		124003	722 / Month 24	0.782	No	
		126001	174 / Month 6	1.700	No	
			357 / Month 12	2.040		
			727 / Month 24	1.480		
		141008	181 / Month 6	1.570	No	
			362 / Month 12	1.940		
			726 / Month 24	2.340		
		141013	715 / Month 24	2.610	Vitritis	Day 0
		143010	722 / Month 24	2.440	No	
		152004	522 / Early Term.	0.752	No	
		153006	183 / Month 6	1.900	No	
			365 / Month 12	1.530		
			718 / Month 24	2.070		
		159017	716 / Month 24	0.780	No	
		167002	717 / Mont 24	1.230	No	
		188005	717 / Month 24	1.250	No	
FVF3192g	**Sham**	534001	-7 / Screening	2.520	Vitritis	Month 1
	Ranibizumab 0.5 mg	507018	357 / Month 12	0.875	No	
		522002	367 / Month 12	1.530	No	

1 In Study FVF2428g, intravitreal injections (sham or ranibizumab 0.5 mg) were given every month and verteporfin PDT every 3 months.
2 Iritis diagnosed 1 day after Month 4 injection.

3 Iritis diagnosed day of injection. Injection was not held.
4 No resolution of uveitis noted in CRFs submitted.
5 Uveitis diagnosed 3 days post Month 7 injection. Serious AE led to treatment discontinuation in Month 9.
6 Treatment discontinued.

Reviewer's Comment:
Fifty subjects in Studies FVF2428g, FVF2587g and FVF2598g had measurable immunoreactivity based upon initial and confirmatory assays. Thirteen of these subjects experienced episodes of intraocular inflammation.

In subjects with an immunoreactivity assay log titer of > 2.00, 31% experienced at least one episode of intraocular inflammation.

In subjects with an immunoreactivity assay log titer of >3.00, 100% experienced an episode of intraocular inflammation.

Appears This Way
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7.1.11 Human Carcinogenicity

Not applicable.

7.1.12 Special Safety Studies

Safety analysis was based on an evaluation of other safety parameters, as well, which included visual acuity (best corrected), intraocular pressure, ocular signs by slit lamp examination and indirect ophthalmoscopy the results of which are included throughout the safety review.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. There was no inadvertent exposure to the product in pregnant women during the development program.

7.1.15 Assessment of Effect on Growth

The intended population for this product is adults with age-related macular degeneration, a disease that does not exist in the pediatric age group. This application contains no pediatric data.

7.1.16 Overdose Experience

This product has no overdose potential and no studies were performed.

7.1.17 Postmarketing Experience

This product has not yet been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

The safety and exposure database for Ranibizumab included in this application is derived from 976 ranibizumab-treated subjects with neovascular age-related macular degeneration, in six clinical trials.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The submitted clinical study reports and clinical protocols related to the development program of ranibizumab were analyzed in this review. Proposed draft labeling and Case Report Forms for discontinued subjects in studies FVF2587g and FVF2598g were provided and reviewed. Refer to Section 4.1.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 for the table of clinical studies.

7.2.1.2 Demographics

Refer to Table 6.1.3.1-9 and Table 6.1.3.2-9 Demographic Statistics by Treatment Group for Studies FVF2598g and FVF2587g.

Reviewer's Comments:

There are no remarkable differences between treatment groups in baseline demographic characteristics.

Subgroup analyses did not reveal any differences in the studies' success on the primary efficacy endpoint.

7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3-1 Extent of Exposure to Study Drug or Sham Injection Safety Evaluable Subjects

	Study FVF2598g			Study FVF2587g		
	Sham PDT N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=238	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
Number of injections [a]						
Mean (SD)	11.7 (2.7)	12.4 (1.9)	12.3 (2.2)	12.0 (2.5)	12.2 (2.1)	12.1 (2.2)
Frequency						
< 10	27 (11.4%)	10 (4.2%)	15 (6.3%)	17 (11.9%)	9 (6.6%)	13 (9.3%)
10-12	55 (23.3%)	36 (15.1%)	40 (16.7%)	21 (14.7%)	29 (21.2%)	29 (20.7%)
13	154 (65.3%)	192 (80.7%)	184 (77.0%)	105 (73.4%)	99 (72.3%)	98 (70.0%)
Treatment duration (days) [b]						
Mean (SD)	332.7 (80.0)	350.6 (54.7)	346.2 (61.5)	337.1 (75.0)	346.2 (61.8)	345.6 (59.7)

a Of 13 scheduled injections from Day 0 to Month 12 visits. The verteporfin PDT group received sham injections.
b The number of days between the first and the last injection on or prior to Month 12 visit.

Reviewer's Comment:
The extent of exposure was similar between all treatment groups in each study. The vast majority of subjects received 10 or more treatment injections. The mean treatment duration ranged from 332.7 days to 350.6 days among the treatment groups.

Table 7.2.1.3-2
Extent of Exposure to Study Treatment with Verteporfin or Sham PDT Safety Evaluable Subjects in the First Treatment Year

	Study FVF2587g		
	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
Number of Treatments			
Mean (SD)	3.1 (1.3)	1.9 (1.3)	1.8 (1.1)
1	18 (12.6%)	76 (55.5%)	79 (56.4%)
2	33 (23.1%)	32 (23.4%)	29 (20.7%)
3	36 (25.2%)	12 (8.8%)	19 (13.6%)
4	26 (18.2%)	5 (3.6%)	9 (6.4%)
5	30 (21.0%)	12 (8.8%)	4 (2.9%)
Treatment duration (days) [b]			
Mean (SD)	228.1 (129.0)	95.8 (129.2)	84.2 (116.3)

a Of 5 possible treatments form Day 0 to Month 12 visits. The ranibizumab groups received sham PDT.
b The number of days between the first and the last treatment on or prior to Month 12 visit.

Table 7.2.1.3-3
Number of Study Drug or Sham Injection Treatments Held
Per Protocol-Specified Criteria During the First Treatment Year
Safety Evaluable Subjects

Injections Held	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
Mean	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)	0.0 (0.2)	0.0 (0.2)	0.2 (0.7)
0	224 (94.9%)	227 (95.4%)	229 (95.8%)	140 (97.9%)	131 (95.6%)	129 (92.1%)
1	7 (3.0%)	9 (3.8%)	7 (2.9%)	2 (1.4%)	6 (4.4%)	6 (4.3%)
2	3 (1.3%)	0	2 (0.8%)	1 (0.7%)	0	3 (2.1%)
3	1 (0.4%)	1 (0.4%)	0	0	0	0
4	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	0	0
5	0	0	0	0	0	2 (1.4%)

Reviewer's Comment:
The vast majority, more than 92% of patients in each treatment group, did not require that treatments be held due to the protocol-specified dose-holding criteria.

Table 7.2.1.3-4
Study Drug or Sham Injection Held per Protocol-Specified Criteria by Criterion Met
First Treatment Year: Safety Evaluable Subjects

Criterion	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239	Verteporfin PDT N=143	Ranibizumab 0.3 mg N=137	Ranibizumab 0.5 mg N=140
Any Treatment Held	**12 (5.1%)**	**11 (4.6%)**	**10 (4.2%)**	**3 (2.1%)**	**6 (4.4%)**	**11 (7.9%)**
Intraocular inflammation	0	2 (0.8%)	4 (1.7%)	0	1 (0.7%)	3 (2.1%)
Visual acuity loss	6 (2.5%)	1 (0.4%)	1 (0.4%)	1 (0.7%)	0	0
IOP elevation	0	0	1 (0.4%)	0	1 (0.7%)	2 (1.4%)
Vitreous hemorrhage	0	2 (0.8%)	0	0	0	0
Sensory rhegmatogenous retinal detachment / break	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.7%)	0
Subfoveal hemorrhage	5 (2.1%)	1 (0.4%)	0	2 (1.4%)	0	2 (1.4%)
Local or systemic infxn	0	4 (1.7%)	2 (0.8%)	0	2 (1.5%)	4 (2.9%)
Intraocular surgery	0	0	2 (0.8%)	0	1 (0.7%)	1 (0.7%)

Note: Tabulation was based on the 13 scheduled injections from Day 0 to Mont 12. Multiple injections that were held because of the same criterion for a given subject were counted once in the overall incidence for the criterion. Multiple occurrences of injections held in a subject were counted once in the overall incidence.

Reviewer's Comment:
Approximately 5% of subjects in each treatment group in Study FVF2598g required that at least one treatment be held due to the protocol-specified dose-holding criteria. In the sham treatment group, the reason for dose holding was most frequently visual acuity loss or subfoveal hemorrhage. In the ranibizumab treatment groups, no single criterion was met in the majority of cases.

In Study FVF2587g, treatments were held for protocol-specified holding criteria least often in the verteporfin PDT group and most frequently in the 0.5 mg ranibizumab group. Intraocular inflammation and local or systemic infection were the most frequent criteria met in the 0.5 mg ranibizumab group.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published litereature.

7.2.2.1 Other studies

No other studies were used to evaluate safety.

7.2.2.2 Postmarketing experience

The product has not yet been marketed. No postmarketing data were used to evaluate safety.

7.2.2.3 Literature

The applicant's literature search was complete, including important issues of safety and efficacy.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate.

The pivotal studies, FVF2587g and FVF2598g, were adequate and well-controlled studies which demonstrated the efficacy of ranibizumab. An adequate number of subjects from relevant demographic groups were exposed to this formulation of ranibizumab to assess potential during the development program. The study designs were appropriate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review for details.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing and monitoring of study subject was adequate to elicit adverse events.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of ranibizumab given by the intravitreal route of administration.

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7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has made adequate efforts to detect specific adverse events for ranibizumab as a biologic and a VEGF inhibitor.

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. There was no imbalance between ranibizumab-treated and sham-treated subjects regarding immunoreactivity to ranibizumab. Refer to Section 7.1.10 for details. Analyses of potential side effects related to systemic VEGF inhibition focused on the incidence of hypertension, arterial thromboembolic events and non-ocular hemorrhage.

Table 7.2.7-1 Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year: Studies FVF2598g and FVF2587g

Type of Adverse Event	Study FVF2598g			Study FVF2587g		
	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239	Verteporfin PDT N=143	Ranibizumab 0.5 mg N=140	Ranibizumab 0.5 mg N=140
TOTAL [a]	**2 (0.8%)**	**8 (3.4%)**	**9 (3.8%)**	**3 (2.1%)**	**4 (2.9%)**	**8 (5.7%)**
Hypertension events	0	1 (0.4%)	0	0	0	0
Arterial thromboembolic events	2 (0.8%)	5 (2.1%)	8 (3.3%)	2 (1.4%)	2 (1.4%)	4 (2.9%)
Non-ocular hemorrhages	0	1 (0.4%)	0	0	2 (1.5%)	3 (2.1%)
Other potentially associated events	0	1 (0.4%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

Reviewer's Comment:

In the two phase 3 studies, a small trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition was noted, particularly in the ranibizumab 0.5-mg dose group. This reflects trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria). No imbalance in overall adverse events potentially related to systemic VEGF inhibition was observed among treatment groups.

7.2.8 Assessment of Quality and Completeness of Data

The data presented were complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The sponsor has submitted the following additional submissions of clinical safety and efficacy data during the review cycle. Amendments 003 and 006 were submitted in response to reviewer requests for additional analyses of the safety database. These amendments have been reviewed individually and the results incorporated into the rest of the review.

- Amendment 003 - Analysis of all of the thromboembolic adverse events in the ranibizumab trials including a comparison of risk factors and concomitant medications between patients who experienced thromboembolic events and all enrolled patients. (Submitted February 17, 2006)
- Amendment 006 – Request for information on all discontinued subjects regardless of attribution to study treatment, all serious adverse events and all adverse events occurring $\geq$ 1% of subjects in any treatment group for both Phase 3 studies. (Submitted March 17, 2006)
- Amendment 008 - Study FVF2598g Year 2 Data and Updated Draft Labeling (Submitted March 31 2006)

On April 28, 2006, the sponsor submitted the 120-Day Safety Update which is considered in this section. This update to the Summary of Clinical Safety includes additional safety information available from Study FVF2598g. Since the submission of the BLA, the collection and cleaning of second-treatment-year data from Study FVF2598g has been completed, and this update includes summaries based on final 2-year data from the study. No additional safety analyses are provided in the SCS update for Study FVF2587g because the trial is still ongoing, or for Study FVF2428g per prior agreement with the FDA. There are no updates to the safety analyses provided for Studies FVF2128g, FVF2425g, and FVF1770g because these trials were complete at the time of the original SCS.

All summaries presented within this report for Study FVF2598g are based on the safety-evaluable population (all subjects who received at least one ranibizumab or sham injection). In addition, subjects are grouped according to the actual treatment received, as defined from the safety analyses presented in the FVF2598g CSR Addendum. Subjects in the sham-injection group who crossed over to receive 0.5 mg ranibizumab per the sixth protocol amendment are included in the safety analyses. These subjects are included in the sham-injection group.

The original SCS included safety data from 1413 subjects, 976 of whom received treatment with ranibizumab. Of the six studies included in the SCS, Study FVF2598g was the largest with a total of 713 safety-evaluable subjects, 477 of whom received treatment with ranibizumab. As summarized in the original SCS, more than 5,800 ranibizumab injections and 2,700 sham injections were administered during the first treatment year of Study FVF2598g.

Table 7.2.9-1 Extent of Study Drug Exposure: Study FVF2598g

	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239
Original SCS			
Number of injections [a]			
Total	2765	2952	2929
Mean (SD) [b]	11.7 (2.7)	12.4 (1.9)	12.3 (2.2)
Treatment duration (days) [c]			
Mean (SD)	332.7 (80.0)	350.6 (54.7)	346.2 (61.5)
Update to SCS			
Number of injections [a]			
Total	4709	5248	5195
Mean (SD) [b]	20.0 (6.3)	22.1 (4.4)	21.7 (5.0)
Treatment duration (days) [c]			
Mean (SD)	590.1 (191.2)	651.4 (130.2)	639.9 (148.2)

a Intravitreal ranibizumab injection or sham injection **b** Number of injections per subject, or 24 scheduled injections during the 2-year treatment period. The summary includes ranibizumab injections received by subjects in the sham-injection group after crossover and a Month 24 injection received by Subject 144001 in the 0.5-mg group. **c** Number of days between the first and the last injection during the study period.

Reviewer's Comments:

The extent of study drug exposure was well balanced between the treatment groups in the first and second years of the study.

Table 7.2.9-3 Treatment and Study Discontinuations during the 2-Year Treatment Period: Safety Evaluable Subjects - Study FVF2598g

	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239
Crossed over to receive 0.5 mg ranibizumab	**12 (5.1%)**	--	--
At Month 22	5 (2.1%)	--	--
At Month 23	7 (3.0%)	--	--
Discontinued treatment [a]	**66 (28.0%)**	**30 (12.6%)**	**32 (13.4%)**
Death	5 (2.1%)	5 (2.1%)	3 (1.3%) [b]
Adverse event	13 (5.5%)	8 (3.4%)	14 (5.9%) [b]
Lost to follow-up	2 (0.8%)	2 (0.8%)	3 (1.3%)
Subject's decision	24 (10.2%)	17 (7.1%)	13 (5.4%)
Physician's decision	1 (0.4%)	1 (0.4%)	2 (0.8%)
Subject non-compliance	1 (0.4%)	0	0
Subject's condition mandated other therapeutic intervention	23 (9.7%)	1 (0.4%)	0

a Some subjects remained in the study after treatment discontinuation.
b Three subjects discontinued from treatment because of an adverse event that resulted in death (the primary reason for study discontinuation).

Table 7.2.9-4 Deaths during the 2-Year Treatment Period: Safety Evaluable Subjects - Study FVF2598g

Time period	Sham	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239
Overall	**6 (2.5%)**	**5 (2.1%)**	**6 (2.5%)**
Year 1	0	1 (0.4%)	2 (0.8%)
Year 2	6 (2.5%)	4 (1.7%)	4 (1.7%)

Table 7.2.9-5 Primary Cause of Deaths that Occurred during the 2-Year Treatment Period: Study FVF2598g

Time period	Treatment Group	Age / Sex	Primary Cause of Death	Study Day	Days Since Last Study Treatment
Year 1 [a]	**0.3 mg**	78/F	Heart attack	12	11
	0.5 mg	78/F	Small bowel infarct	178	24
		90/F	Chronic asthma / COPD	155	2
Year 2	**Sham**	74/F	Unknown cause	481	3
		88/M	Congestive heart failure	724	91
		76/F	Cerebrovascular accident	673	35
		77/M	Acute or chronic renal failure	656	45
		80/M	Cerebral vascular accident; bilateral parietal lobe and cerebellum	576	31
		71/M	Acute respiratory failure	400	67
	0.3 mg	91/F	Unknown	669	99
		77/F	Complications of Non-Hodgkin's Lymphoma	752	425
		91/F	Myocardial infarction	570	23
		81/M	Pneumonia	617	47
	0.5 mg	72/M	Closed head injury resulting from automobile accident	627	57
		87/F	Stroke	667	461
		76/M	Sepsis	496	16
		85/F	Hemorrhagic cerebrovascular accident	428	14

Reviewer's Comment:
An additional 14 deaths occurred in the second treatment year. Overall, no imbalance was noted between the treatment groups in the numbers or causes of death during the 2 year treatment period. The primary causes of death were common events in this elderly population of patients.

Table 7.2.9-6 Ocular Serious Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in > 1 Subject Overall): Study FVF2598g

MedDRA Preferred Term	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239
Total Ocular Events in the Study Eye [a]	**17 (7.2%)**	**20 (8.4%)**	**21 (8.8%)**
Choroidal neovascularization	2 (0.8%)	0	0
Detachment of RPE	0	1 (0.4%)	1 (0.4%)
Endophthalmitis	0	2 (0.8%)	2 (0.8%)
IOP increased	0	1 (0.4%)	2 (0.8%)
Iridocyclitis	0	1 (0.4%)	2 (0.8%)
Macular degeneration	6 (2.5%)	1 (0.4%)	2 (0.8%)
Medication error	0	1 (0.4%)	1 (0.4%)
Retinal detachment	1 (0.4%) [b]	1 (0.4%) [c]	0
Retinal hemorrhage	4 (1.7%)	2 (0.8%)	1 (0.4%)
Retinal tear	0	1 (0.4%)	1 (0.4%)
Uveitis	0	1(0.4%)	1 (0.4%)
Visual acuity reduced	3 (1.3%)	3 (1.3%)	1 (0.4%)
Vitreous hemorrhage	2 (0.8%)	1 (0.4%)	1 (0.4%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye.
b Rhegmatogenous retinal detachment
c Exudative retinal detachment

Reviewer's Comment:
Generally, serious ocular adverse events occurred in a very low percentage of subjects regardless of treatment group. The results are similar to those seen in the first treatment year.

Given the numbers of intravitreal injections in each treatment group (See Table 7.2.9-1), the per-injection rates of endophthalmitis, traumatic cataract, intraocular inflammation and retinal detachment were all very low approximately ≤ 0.10% per injection in each dose group.

Conjunctival hemorrhage, increased intraocular pressure, vitreous floaters, and vitritis occurred more frequently in the ranibizumab groups than in the sham injection group.

Choroidal neovascularization, macular degeneration, retinal hemorrhage, and subretinal fibrosis, manifestations of active neovascular AMD lesions were more common in the sham-injection group than in the ranibizumab groups.

Table 7.2.9-7 Non-Ocular Serious Adverse Events during the 2-Year Treatment Period (Occurring in > 1 Subject Overall): Study FVF2598g

MedDRA Preferred Term	Ranibizumab 0.5 mg N=238	Ranibizumab 0.5 mg N=239
Total Non-Ocular Events	**73 (30.9%)**	**82 (34.5%)**	**76 (31.8%)**
Abdominal pain upper	3 (1.3%)	0	0
Acute myocardial infarction	0	3 (1.3%) [b]	0
Angina unstable	0	2 (0.8%)	0
Arthritis	0	2 (0.8%)	0
Asthma	1 (0.4%)	1 (0.4%)	2 (0.8%)
Atrial fibrillation	4 (1.7%)	3 (1.3%)	5 (2.1%)
B-cell lymphoma	2 (0.8%)	0	0
Back pain	0	2 (0.8%)	0
Breast cancer	2 (0.8%)	0	0
Cardiac failure congestive	6 (2.5%)	4 (1.7%)	1 (0.4%)
Carotid artery stenosis	0	0	2 (0.8%)
Cellulitis	5 (2.1%)	1 (0.4%)	0
Cerebrovascular accident	3 (1.3%)	3 (1.3%)	6 (2.5%)
Chest pain	3 (1.3%)	4 (1.7%)	3 (1.3%)
Chronic obstructive pulmonary disease	2 (0.8%)	4 (1.7%)	4 (1.7%)
Coronary artery disease	5 (2.1%)	2 (0.8%0	4 (1.7%)
Coronary artery occlusion	1 (0.4%)	0	2 (0.8%)
Deep vein thrombosis	0	3 (1.3%)	0
Dehydration	0	1 (0.4%)	2 (0.8%)
Diverticulitis	1 (0.4%)	2 (0.8%)	4 (1.7%)
Gout	2 (0.8%)	0	0
Hip fracture	1 (0.4%)	5 (2.1%)	1 (0.4%)
Lobar pneumonia	1 (0.4%)	2 (0.8%)	0
Lumbar spinal stenosis	2 (0.8%)	0	0
Lung neoplasm malignant	3 (1.3%)	2 (0.8%)	2 (0.8%)
Myocardial infarction	4 (1.7%)	4 (1.7%)	2 (0.8%)
Non-cardiac chest pain	0	0	2 (0.8%)
Osteoarthritis	3 (1.3%)	1 (0.4%)	0
Pneumonia	4 (1.7%)	9 (3.8%)	7 (2.9%)
Renal cell carcinoma stage unspecified	2 (0.8%)	0	0
Sepsis	0	0	3 (1.3%)
Syncope	6 (2.5%)	3 (1.3%)	2 (0.8%)
Transient ischemic attack	1 (0.4%)	2 (0.850	3 (1.3%)

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one non-ocular serious adverse event.
b Includes Subject 101020 with a serious adverse event of acute myocardial infarction even though the event was removed from final study database based on a investigator correction form submitted after the completion of the FVF2598g CS.
c The sham-treated subject (118004) who experiences a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. **d** Includes one case reported as a cerebral ischemia.

Reviewer's Comment:
The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The percentages of subjects with non-ocular serious adverse events were well balanced among the treatment groups and similar to those seen in the first treatment year.

Table 7.2.9-8 Ocular Adverse Events in the Study Eye that Led to Discontinuation from Study or from Treatment during the 2-Year Treatment Period: Study FVF2598g

MedDRA Preferred Term	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239
Total [a]	**15 (6.4%)**	**6 (2.5%)**	**7 (2.9%)**
Choroidal neovascularization	7 (3.0%)	0	0
Conjunctivitis allergic	0	0	1 (0.4%)
Eye pain	0	0	2 (0.8%)
Glaucoma	0	0	1 (0.4%)
Hypopyon	0	0	1 (0.4%)
Iridocyclitis	0	0	2 (0.8%)
Iris adhesions	0	0	1 (0.4%)
Iritis	0	3 (1.3%)	0
Macular degeneration	6 (2.5%)	0	0
Macular hole	0	1 (0.4%)	0
Maculopathy	0	1 (0.4%)	0
Retinal detachment	1 (0.4%)	0	0
Retinal hemorrhage	4 (1.7%)	1 (0.4%)	0
Retinal tear	1 (0.4%)	0	0
Uveitis	0	0	2 (0.8%)
Visual acuity reduced	2 (0.8%)	0	0
Vitreous detachment	1 (0.4%)	0	0
Vitreous floaters	0	0	1 (0.4%)
Vitritis	0	0	1 (0.4%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye that led to discontinuation of study or treatment.

Reviewer's Comment:
There was a larger discontinuation rate in the sham-injection group than in either ranibizumab group usually due to signs and symptoms of worsening macular degeneration.

Ranibizumab group discontinuations were caused by signs and symptoms that may be associated with intraocular inflammation. These findings are similar to those in the first treatment year.

Table 7.2.9-9 Ocular Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in ≥ 10% of Subjects in Any Group): Study FVF2598g

MedDRA Preferred Term		Ranibizumab	
		0.5 mg N=238	0.5 mg N=239
Total [a]	**234 (99.2%)**	**236 (99.2%)**	**235 (98.3%)**
Blepharitis	21 (8.9%)	26 (10.9%)	32 (13.4%)
Cataract NOS [b]	37 (15.7%)	37 (15.5%)	37 (15.5%)
Choroidal neovascularization	40 (16.9%)	1 (0.4%)	4 (1.7%)
Conjunctival hemorrhage	156 (66.1%)	184 (77.3%)	181 (75.7%)
Detachment of RPE	36 (15.3%)	27 (11.3%)	22 (9.2%)
Dry eye	15 (6.4%)	16 (6.7%)	24 (10.0%)
Eye irritation	47 (19.9%)	38 (16.0%)	46 (19.2%)
Eye pain	79 (33.5%)	86 (36.1%)	89 (37.2%)
Eye pruritus	29 (12.3%)	23 (9.7%)	32 (13.4%)
Foreign body sensation in eyes	34 (14.4%)	43 (18.1%)	45 (18.8%)
Intraocular inflammation [c]	25 (10.6%)	33 (13.9%)	43 (18.0%)
IOP increased	14 (5.9%)	57 (23.9%)	57 (23.8%)
Lacrimation increased	38 (16.1%)	41 (17.2%)	39 (16.3%)
Macular degeneration	159 (67.4%)	111 (46.6%)	109 (45.6%)
Macular edema	27 (11.4%)	6 (2.5%)	12 (5.0%)
Maculopathy	27 (11.4%)	20 (8.4%)	23 (9.6%)
Ocular hyperemia	24 (10.2%)	24 (10.1%)	24 (10.0%)
Retinal degeneration	16 (6.8%)	25 (10.5%)	24 (10.0%)
Retinal disorder	22 (9.3%)	27 (11.3%)	30 (12.6%)
Retinal exudates	25 (10.6%)	21 (8.8%)	16 (6.7%)
Retinal hemorrhage	132 (55.9%)	61 (25.6%)	58 (24.3%)
Subretinal fibrosis	37 (15.7%)	22 (9.2%)	15 (6.3%)
Vision blurred	20 (8.5%)	34 (14.3%)	22 (9.2%)
Visual acuity reduced	39 (16.5%)	26 (10.9%)	24 (10.0%)
Visual disturbance	21 (8.9%)	27 (11.3%)	33 (13.8%)
Vitreous detachment	42(17.8%)	52 (21.8%)	53 (22.2%)
Vitreous floaters	24 (10.2%)	76 (31.9%)	71 (29.7%)
Vitritis	8 (3.4%)	17 (7.1%)	30 (12.6%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye. b Includes the preferred terms: cataract, cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities. c Includes the preferred terms anterior chamber inflammation, hypopyon, iridocyclitis, iritis, uveitis and vitritis.

Reviewer's Comment:

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. Conjunctival hemorrhage, increased intraocular pressure, vitreous floaters, and vitritis occurred more frequently in the ranibizumab groups than in the sham injection group. These findings are similar to those in the first treatment year.

Choroidal neovascularization, macular degeneration, retinal hemorrhage, and subretinal fibrosis, manifestations of active neovascular AMD lesions were more common in the sham-injection group than in the ranibizumab groups.

The apparent dose dependent trend in the incidence of intraocular inflammation adverse events in the study eye was slightly increased in the 2-year treatment period data. Seven of the ranibizumab-treated subjects (1.5%) experienced at least one serious intraocular inflammation adverse event in the study eye. All of the serious intraocular inflammation adverse events were considered by the investigator to be related to study drug. Six of the seven subjects had study treatment held or discontinued from study treatment because of serious intraocular inflammation. One subject in the ranibizumab 0.5-mg group was reported to have serious uveitis and was treated with intravitreal antibiotics. The sponsor considered this adverse event a presumed case of endophthalmitis.

Elevated intraocular pressure adverse events were noted more frequently in the ranibizumab treated groups. Most events were reported as mild or moderate in severity though three ranibizumab-treated subjects had severe events. For those events that required treatment, medication was used most frequently though paracenteses and anterior chamber taps were required in eight of the 305 reported events.

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Table 7.2.9-10 Non-Ocular Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in ≥ 5% of Subjects in Any Group): Study FVF2598g

MedDRA Preferred Term	[redacted]	Ranibizumab 0.5 mg N=238	Ranibizumab 0.5 mg N=239
Total [a]	**214 (90.7%)**	**228 (95.8%)**	**228 (95.8%)**
Anemia	19 (8.1%)	17 (7.1%)	18 (7.5%)
Anxiety	7 (3.0%)	10 (4.2%)	12 (5.0%)
Arthralgia	21 (8.9%)	26 (10.9%)	27 (11.3%)
Arthritis	20 (8.5%)	17 (7.1%)	19 (7.9%)
Back pain	22 (9.3%)	24 (10.1%)	22 (9.2%)
Blood pressure increased	18 (7.6%)	16 (6.7%)	20 (8.4%)
Bronchitis	20 (8.5%)	23 (9.7%)	25 (10.5%)
Chest pain	13 (5.5%)	10 (4.2%)	9 (3.8%)
Constipation	18 (7.6%)	15 (6.3%)	13 (5.4%)
Contusion	20 (8.5%)	10 (4.2%)	9 (3.8%)
Cough	17 (7.2%)	23 (9.7%)	25 (10.5%)
Depression	16 (6.8%)	12 (5.0%)	14 (5.9%)
Diarrhea	20 (8.5%)	18 (7.6%)	10(4.2%)
Dizziness	23 (9.7%)	18 (7.6%)	11 (4.6%)
Dyspnea	6 (2.5%)	12 (5.0%)	8 (3.3%)
Edema peripheral	14 (5.9%)	17 (7.1%)	10 (4.2%)
Gastroesophageal reflux disease	12 (5.1%)	15 (6.3%)	9 (3.8%)
Headache	24 (10.2%)	36 (15.1%)	24 (10.0%)
Herpes zoster	5 (2.1%)	13 (5.5%)	10 (4.2%)
Hypercholesterolemia	11 (4.7%)	10 (4.2%)	13 (5.4%)
Hypertension	38 (16.1%)	41 (17.2%)	39 (16.3%)
Influenza	12 (5.1%)	23 (9.7%)	19 (7.9%)
Insomnia	13 (5.5%)	10 (4.2%)	14 (5.9%)
Nasopharyngitis	31 (13.1%)	32 (13.4%)	38 (15.9%)
Nausea	13 (5.5%)	21 (8.8%)	21 (8.8%)
Pain in extremity	14 (5.9%)	15 (6.3%)	13 (5.4%)
Pneumonia	13 (5.5%)	18 (7.6%)	11 (4.6%)
Sinusitis	13 (5.5%)	18 (7.6%)	20 (8.4%)
Upper respiratory tract infection	23 (9.7%)	36 (5.1%)	18 (7.5%)
Urinary tract infection	18 (7.6%)	21 (8.8%)	17 (7.1%)

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.
a Represents the number of subjects with at least one ocular adverse event in the study eye.

Reviewer's Comment:

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The reported adverse events during the 2-year treatment period were consistent with those seen in an elderly population and the first treatment year results.

Reviewer's Comment:
The overall 2-year safety profile in Study FVF2598g was similar to that observed based on first-treatment-year data. The most common adverse events in the study eye observed more frequently in the ranibizumab groups than in the sham-injection group were conjunctival hemorrhage, increased intraocular pressure and vitreous floaters.

The dose dependent association of ranibizumab and intraocular inflammation noted during the first treatment year persisted in the second treatment year. Cumulative 2-year rates of reported intraocular inflammation adverse events in the study eye of 13.9% and 18.0% in the 0.3-mg and 0.5-mg ranibizumab groups compared with the sham-injection group, 10.6%. The observed intraocular inflammation adverse events were usually mild in severity and occurrence was well-balanced among the subgroups studied. Serious intraocular inflammation adverse events only occurred in the ranibizumab groups with a cumulative rate of ≤ 1.7% during the 2-year treatment period.

Table 7.2.9-11 APTC Arterial Thromboembolic Events during the 2-Year Treatment Period: Safety-Evaluable Subjects - Study FVF2598g

Event Type	Sham N=236	Ranibizumab 0.3 mg N=238	Ranibizumab 0.5 mg N=239
Total	**9 (3.8%)**	**11 (4.6%)**	**11 (4.6%)**
Vascular deaths	4 (1.7%) [a]	3 (1.3%) [b]	3 (1.3%)
Nonfatal myocardial infarction	4 (1.7%)	6 (2.5%) [c]	3 (1.3%)
Nonfatal ischemic stroke	2 (0.8%) [a, e]	3 (1.3%) [b]	5 (2.1%) [f]
Nonfatal hemorrhagic stroke	0	0	1 (0.4%) [d]

Note: Antiplatelet Trialists' Collaboration. BMJ. 1994 Jan 8; 308(6921):81-106.
a Subject 136007 had a prior non-fatal ischemic stroke.
b Subject 101019 had a non-fatal ischemic stroke and died of an unknown cause.
c Subject 109001 had two events of MI.
d Subject 158001 had an MI and a hemorrhagic stoke, both non-fatal.
e The sham-treated subject (118004) who suffered a subacute parietooccipital lobe CVA (reported as an ocular serious adverse event) had received a single injection of ranibizumab 0.5 mg in error approximately 8 months prior to the stroke.
f Include 1 subject (200001) with cerebral ischemia who had MRI evidence of infarction I the pons and thalamus.

Reviewer's Comment:
In the second treatment year, the trend toward higher rates of APTC arterial thromboembolic events was somewhat decreased because the number of subjects who experienced events in the second treatment year was similar among the treatment groups (1 subjects [3.2%] in the sham-injection group, 8 subjects [3.4%] in the 0.3 mg ranibizumab group, and 6 subjects [2.6%] in the 0.5 mg ranibizumab group).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The trend in intraocular inflammation adverse events observed during the first treatment year was also observed through the second treatment year of Study FVF2598g, with cumulative 2-year rates of reported intraocular inflammation adverse events in the study eye of 13.9% and 18.0% in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with 10.6% in the sham-injection group. However, the reported intraocular inflammation adverse events were generally mild in severity. The incidence of intraocular inflammation adverse events did not differ substantially between the subgroups examined, and rates were lower in the second treatment year compared with the first treatment year. The incidence of intraocular inflammation adverse events was consistent with results based on slit lamp examination.

In Study FVF2598g, serious intraocular inflammation adverse events were observed only in the ranibizumab groups but were uncommon for both dose groups (≤ 1.7% cumulative rate over the 2-year treatment period).

The frequency of intraocular inflammation adverse events in the study eye was higher in the ranibizumab groups (10.2% in the 0.3-mg group and 15.0% in the 0.5-mg group) compared with the verteporfin PDT group (2.8%).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Table 7.4.1.1-1 Arterial Thromboembolic Events during the First Treatment Year: Studies FVF2598g and FVF2587g Pooled (Safety Evaluable Subjects)

MedDRA Preferred Term	Control N=396	Ranibizumab 0.3 mg N=375	Ranibizumab 0.5 mg N=379
Total [a]	**11 (2.9%)**	**11 (2.9%)**	**15 (4.0%)**
Acute Coronary Syndrome	0	1 (0.3%)	0
Acute myocardial infarction	0	1 (0.3%)	0
Angina pectoris	2 (0.5%)	3 (0.8%)	2 (0.5%)
Angina unstable	0	1 (0.3%)	0
Cerebral infarction	0	1 (0.3%)	0
Cerebral ischemia	0	0	1 (0.3%)
Cerebrovascular accident	2 (0.5%) [b]	1 (0.3%)	3 (0.8%)
Embolism	0	0	1 (0.3%)
Femoral artery occlusion	1 (0.3%)	0	0
Intestinal infarction	0	0	1 (0.3%)
Myocardial infarction	2 (0.5%)	2 (0.5%)	4 (1.1%)
Retinal artery occlusion	0	1 (0.3%)	0

MedDRA Preferred Term	Control N=379	Ranibizumab 0.3 mg N=375	Ranibizumab 0.5 mg N=379
Transient ischemic attack	4 (1.1%)	0	4 (1.1%)
Vascular graft occlusion	0	1 (0.3%)	0
Vascular occlusion	0	1 (0.3%)	0

a Represents the number of subjects with at least one arterial thromboembolic event.
b A sham-treated subject in Study FVF2598g who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event.

Reviewer's Comment:

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The number of subjects with an arterial thromboembolic event was small in the pooled analysis of studies FVF2598g and FVF2587g. A direct relationship between ranibizumab dose and arterial thromboembolic events can not be ruled out.

A sham-treated subject in Study FVF2598g who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event.

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Table 7.4.1.1-2 Potential Risk Factors and Baseline Concomitant Medication Use for Subjects with Arterial Thromboembolic Events versus All Subjects: Studies FVF2598g and FVF2587g Pooled (Safety-Evaluable Subjects)

	Control		Ranibizumab			
			0.3 mg		0.5 mg	
	Subjects w/ ATE n=11[a]	All Subjects n=379	Subjects w/ ATE n=11	All Subjects n=375	Subjects w/ ATE n=15	All Subjects n=379
Potential Risk Factor						
Age ≥ 75 years	8 (72.7%)	259 (68.3%)	8 (72.7%)	262 (69.9%)	12 (80.0%)	244 (64.4%)
Male	7 (63.6%)	143 (37.7%)	2 (18.2%)	156 (41.6%)	5 (33.3%)	163 (43.0%)
History of hypertension or hypertension at baseline [b]	7 (63.6%)	249 (65.7%)	9 (1.8%)	265 (70.7%)	10 (66.7%)	263 (69.4%)
History of ATE	6 (54.5%)	112 (29.6%)	8 (72.7%)	117 (31.2%)	7 (46.7%)	107 (28.2%)
History of atherosclerosis	7 (63.6%)	125 (33.0%)	9 (81.8%)	127 (33.9%)	7 (46.7%)	124 (32.7%)
History of diabetes mellitus	3 (27.3%)	46 (12.1%)	4 (36.4%)	47 (12.5%)	3 (20.0%)	59 (15.6%)
History of myocardial infarction	1 (9.1%)	29 (7.7%)	2 (18.2%)	22 (5.9%)	3 (20.0%)	27 (7.1%)
History of stroke or TIA	2 (18.2%)	31 (8.2%)	3 (27.3%)	26 (6.9%)	3 (20.0%)	28 (7.4%)
History of venous thrombosis	0	9 (2.4%)	1 (9.1%)	13 (3.5%)	1 (6.7%)	13 (3.4%)
Baseline concomitant medication use						
Aspirin	6 (54.5%)	161 (42.5%)	4 (36.4%)	146 (38.9%)	7 (46.7%)	142 (37.5%)
Persantine	0	0	0	0	0	0
Anti-platelet agents	4 (36.4%)	167 (44.1%)	9 (81.8%)	168 (44.8%)	5 (33.3 %)	176 (46.4%)
Anti-coagulant agents	2 (18.2%)	27 (7.1%)	1 (9.1%)	26 (6.9%)	1 (6.7%)	18 (4.7%)
Lipid-lowering agents	4 (36.4%)	153 (40.4%)	5 (45.5%)	150 (40.0%)	3 (20.0%)	151 (39.8%)

a A sham-treated subject in Study FVF2598g who experienced a subacute parieto-occipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. **b** Hypertension at baseline was defined as systolic blood pressure >150 mmHg, diastolic blood pressure > 100 mmHg, or a use of a concomitant medication indicated for hypertension.

Reviewer's Comment:

For all subjects, potential risk factors for ATEs and baseline concomitant medication use were well balanced across the treatment groups in terms of percentages.

The number of subjects with ATE was small making comparisons somewhat difficult. Though subjects in the ranibizumab 0.5 mg group with an ATE did not have the highest aspirin use, their aspirin use was higher than all subjects in the ranibizumab 0.5 mg group.

Subjects with an ATE in the ranibizumab 0.5 mg group generally had potential risk factors at a higher percentage than the group as a whole.

7.4.1.2 Combining data

Studies FVF2598g and FVF2587g were sufficiently similar to allow data to be combined by adding the numerator events and denominators of the treatment groups across the studies.

7.4.2 Explorations for Predictive Factors

A detailed discussion of the adverse events is presented in Sections 7.1.1 through 7.1.6. No clear predictive factors for a drug-related adverse event were identified.

7.4.3 Causality Determination

Due to the small number of patients, no determination of causality could be made regarding the adverse events in the Phase 3 studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor has performed adequate dose ranging studies during the drug development program. Lucentis (ranibizumab) 0.5 mg dose has been demonstrated to be safe and effective in two Phase 3 clinical trials. The dosing interval in the two pivotal Phase 3 trials was once monthly resulting in the improvement and maintenance of visual acuity and function, and for the reduction of vascular leakage and retinal edema, in patients with neovascular (wet) age-related macular degeneration.

8.2 Drug-Drug Interactions

No important drug-drug interactions have been identified.

8.3 Special Populations

The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Subgroup analyses did not reveal any differences in the primary efficacy endpoint between males and females. The safety profiles seen in males and females, including the types and rates of adverse events, are similar.

Trials for this indication were conducted in a population that was overwhelmingly elderly and Caucasian. This is reflective of the population in which age-related macular degeneration occurs and does not reflect a problem with study enrollment.

8.4 Pediatrics

The applicant requested a waiver of the pediatric study requirements for the original Biologics License Application. The waiver was requested because the disease under study age-related macular degeneration does not occur in the pediatric age group.

8.5 Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting will be held regarding this application.

8.6 Literature Review

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan has been submitted.

8.8 Other Relevant Materials

Comments received from DDMAC and the Office of Drug Safety have been incorporated in the labeling review as appropriate.

9 OVERALL ASSESSMENT

9.1 Conclusions

The submitted studies in BLA 125156 are sufficient to establish efficacy for the use of ranibizumab 0.5 mg injection in the treatment of the neovascular age-related macular degeneration. The two Phase 3 studies provide replicative demonstration that monthly ranibizumab injections are able to stabilize and prevent vision loss in patients with neovascular macular degeneration compared to monthly sham and verteporfin PDT treatment.

9.2 Recommendation on Regulatory Action

BLA 125156 is recommended for approval from a clinical perspective for the treatment of patients with neovascular (wet) age-related macular degeneration with the labeling revisions within this review.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not applicable. No postmarketing risk management activity is recommended at this time.

9.3.2 Required Phase 4 Commitments

1. Develop and validate assays to detect and characterize immune responses to ranibizumab:

A. Develop and validate a confirmatory assay capable of detecting both IgG and IgM isotype responses.

B. Develop and validate an assay to detect neutralizing anti-ranibizumab antibodies.

The assay methodology and validation reports will be provided by September 28, 2007.

2. To characterize further the immune response to ranibizumab, serum samples collected in studies FVF2587g, FVF2598g, FVF3192g will be assayed using the validated methods described above in Postmarketing Commitment . The data obtained will be analyzed to discover and evaluate any association between immunoreactivity and dosing frequency as well as any potential impact of immunoreactivity on efficacy or safety outcomes.

   Date of submission of protocol and statistical analysis plan: February 28, 2007

   Date of submission of final study report: September 2008.

3. The need for an additional clinical study will be determined based on the results from the analysis described above..

9.3.3 Other Phase 4 Requests

Not applicable. There are no additional Phase 4 requests.

9.4 Labeling Review

Refer to the Appendix, Section 10.2 for the medical officer's labeling review.

9.5 Comments to Applicant

There are no comments pertaining to specific deficiencies.

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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 6444