CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125156/S053

Trade Name: Lucentis®

Generic Name: RANIBIZUMAB

Sponsor: Genentech

Approval Date: 6/22/2010

Indication: LUCENTIS is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD) and Macular Edema Following Retinal Vein Occlusion (RVO).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

CONTENTS

Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Submission Tracking Number (STN): BLA 125156/053

APPROVAL
June 22, 2010

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, California 94080-4990

Dear Dr. Rohrer:

Please refer to your supplement to your biologics license application (BLA), dated December 18, 2009, received December 22, 2009, submitted under section 351 of the Public Health Service Act for Lucentis (ranibizumab injection). We acknowledge receipt of your amendments dated April 16, May 5, June 21 and 22, 2010. Your request to supplement your BLA for Lucentis (ranibizumab injection) to include the new indication, Macular Edema Following Retinal Vein Occlusion (RVO), has been approved.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application because studies would be impossible or highly impracticable as there are too few pediatric patients with macular edema following a retinal vein occlusion.

We acknowledge your written commitments as described in your letter of June 22, 2010, as outlined below:

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

1. Provide safety and efficacy data on at least 150 patients with macular edema following a retinal vein occlusion, followed for at least 15 months and randomized sometime within 15 months of their first treatment with Lucentis. Patients must receive 7 monthly doses of Lucentis, be evaluated monthly for the need of additional doses of Lucentis based on OCT and visual acuity criteria and if determined to not need an additional monthly dose

of Lucentis be randomized to receive an additional dose or not to receive an additional dose of Lucentis.

Final Protocol Submission: November 1, 2010

Study Start Date: March 1, 2011

Final Report Submission: October 1, 2013

We request that you submit the clinical protocol to your IND, with a cross-reference letter to this BLA, STN **[125156/053]**. Submit the final report to this BLA. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKEING COMMITMENT – FINAL REPORT**
- **POSTMARKETING CORRESPONDENCE**
- **ANNUAL STATUS REPORTING OF POSTMARKETING COMMITMENTS**

For each postmarketing commitment subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report. The status report for each commitment should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including the patient accrual rate (i.e., number enrolled to date and the total planned enrollment); and,
- a revised schedule if the scheduled milestones have changed and an explanation of the basis for the revision.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

2. Submit the final Clinical Study Reports from the 6 month observation periods for Study FVF4165g and FVF4166g.

   Final Report Submission: October 1, 2010

3. Submit the final Clinical Study Reports from Study FVF3426g.

   Final Report Submission: November 1, 2011

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

If you have any questions, call Lori Marie Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection)
Intravitreal Injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

- Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.2), 6/2010
- Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (RVO) (2.3), 6/2010
- Warnings and Precautions, Thromboembolic Events (5.3), 6/2010

----------INDICATIONS AND USAGE----------

LUCENTIS is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)

----------DOSAGE AND ADMINISTRATION----------

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days) (2.2).
- Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly (2.2).

Macular Edema Following Retinal Vein Occlusion (RVO)

- LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days). In the RVO clinical studies, patients received monthly injections of LUCENTIS for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

- 10 mg/mL solution in a single-use vial for intravitreal injection (3)

----------CONTRAINDICATIONS----------

- Ocular or periocular infections (4.1)
- Hypersensitivity (4.2)

----------WARNINGS AND PRECAUTIONS----------

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored during the week following the injection (5.1).
- Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection (5.2).

----------ADVERSE REACTIONS----------

- The most common adverse reactions (reported more frequently in LUCENTIS-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure, and intraocular inflammation (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information
FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly [*see Clinical Studies (14.2)*].

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

In Studies RVO-1 and RVO-2, patients received monthly injections of LUCENTIS for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly [*see Clinical Studies (14.2)*].

2.4 Preparation for Administration
Using aseptic technique, all (0.2 mL) of the LUCENTIS vial contents are withdrawn through a 5-micron, 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

2.5 Administration
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before LUCENTIS is administered to the other eye.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS
Single-use glass vial designed to provide 0.05 mL of 10 mg/mL solution for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored during the week following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.4, 2.5) and Patient Counseling Information (17)*].

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection with LUCENTIS. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.5)*].

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies during the first year was 1.9% (17 out of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 out of 441) in patients from the control arms [*see Clinical Studies (14.1)]*. In the second year of studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 out of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 out of 344) in patients from the control arms.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2 and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 out of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 out of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first six months was 0.8% in both the LUCENTIS and control arms of the studies (4 out of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 out of 260 in the control arms) [*see Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 out of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 out of 260) in the control arms.

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis [*see Warnings*

and Precautions (5.1)], rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts.

6.2 Clinical Studies Experience

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in three double-masked, controlled studies (AMD-1, AMD-2, and AMD-3) [*see Clinical Studies (14.1)*] as well as exposure to 0.5 mg LUCENTIS in 259 patients with macular edema following RVO in two double-masked, controlled studies (RVO-1 and RVO-2) [*see Clinical Studies (14.2)*].

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS treated patients compared with the control group.

Table 1
Ocular Reactions in AMD and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS n=379	Control n=379	LUCENTIS n=440	Control N=441	LUCENTIS n=259	Control n=260
Conjunctival hemorrhage	74%	60%	64%	50%	48%	37%
Eye pain	35%	30%	26%	20%	17%	12%
Vitreous floaters	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	24%	7%	17%	5%	7%	2%
Vitreous detachment	21%	19%	15%	15%	4%	2%
Intraocular inflammation	18%	8%	13%	7%	1%	3%
Cataract	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	16%	14%	13%	10%	7%	5%
Eye irritation	15%	15%	13%	12%	7%	6%
Lacrimation increased	14%	12%	8%	8%	2%	3%
Blepharitis	12%	8%	8%	5%	0%	1%
Dry eye	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	18%	15%	13%	10%	5%	3%
Eye pruritis	12%	11%	9%	7%	1%	2%
Ocular hyperemia	11%	8%	7%	4%	5%	3%
Retinal disorder	10%	7%	8%	4%	2%	1%
Maculopathy	9%	9%	6%	6%	11%	7%
Retinal degeneration	8%	6%	5%	3%	1%	0%
Ocular discomfort	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Table 2 shows frequently reported non-ocular adverse reactions in LUCENTIS treated patients compared with the control group.

Table 2

Non-Ocular Reactions in AMD and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS n=379	Control n=379	LUCENTIS n=440	Control n=441	LUCENTIS n=259	Control n=260
Nasopharyngitis	16%	13%	8%	9%	5%	4%
Headache	12%	9%	6%	5%	3%	3%
Arthralgia	11%	9%	5%	5%	2%	1%
Bronchitis	11%	9%	6%	5%	0%	2%
Urinary tract infection	9%	9%	5%	5%	1%	2%
Cough	9%	8%	5%	4%	2%	2%
Nausea	9%	6%	5%	5%	1%	2%
Upper respiratory tract infection	9%	8%	5%	5%	2%	2%
Sinusitis	8%	7%	5%	5%	3%	2%
Anemia	8%	7%	4%	3%	1%	1%
Influenza	7%	5%	3%	2%	3%	2%
Chronic obstructive pulmonary disease	6%	3%	1%	0%	0%	0%
Hypercholesterolemia	5%	5%	3%	2%	1%	1%
Insomnia	5%	5%	3%	2%	1%	1%
Pain in extremity	5%	6%	3%	2%	1%	1%
Atrial fibrillation	5%	4%	2%	2%	1%	0%
Anxiety	4%	4%	3%	2%	1%	2%
Dyspnea	4%	3%	2%	2%	0%	0%
Gastroenteritis viral	4%	1%	3%	1%	1%	0%

6.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%–5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-8% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in the RVO patients with the highest levels of immunoreactivity.

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (±2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with ranibizumab. It is also not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LUCENTIS should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ranibizumab is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of LUCENTIS in pediatric patients has not been established.

8.5 Geriatric Use

In the clinical studies, approximately 82% (1146/1406) of the patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 55% (772/1406) were ≥ 75 years of age. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure in population pharmacokinetic analyses after correcting for creatinine clearance.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with renal impairment. In population pharmacokinetic analyses of patients, 54% (389/725) had renal impairment (39% mild, 12% moderate, and 2% severe). The reduction in ranibizumab clearance in patients with renal impairment is considered clinically insignificant. Dose adjustment is not expected to be needed for patients with renal impairment.

8.7 Patients with Hepatic Dysfunction

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with hepatic impairment. Dose adjustment is not expected to be needed for patients with hepatic dysfunction.

10 OVERDOSAGE

Planned initial single doses of ranibizumab injection 1 mg were associated with clinically significant intraocular inflammation in 2 of 2 neovascular AMD patients injected. With an escalating regimen of doses beginning with initial doses of ranibizumab injection 0.3 mg, doses as high as 2 mg were tolerated in 15 of 20 neovascular AMD patients.

11 DESCRIPTION

LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

LUCENTIS is a sterile, colorless to pale yellow solution in a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL LUCENTIS aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to the progression of neovascular AMD and macular edema following RVO. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

12.2 Pharmacodynamics

Increased center point thickness (CPT) as assessed by optical coherence tomography (OCT) is associated with neovascular AMD and macular edema following RVO. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography is associated with neovascular AMD.

Neovascular (Wet) Age-Related Macular Degeneration

In Study AMD-3, CPT was assessed by OCT in 118/184 patients. OCT measurements were collected at baseline, Months 1, 2, 3, 5, 8, and 12. In patients treated with LUCENTIS, CPT decreased, on average, more than the sham group from baseline through Month 12. CPT decreased by Month 1 and decreased further at Month 3, on average. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.1)*].

In patients treated with LUCENTIS, the area of vascular leakage, on average, decreased by Month 3 as assessed by fluorescein angiography. The area of vascular leakage for an individual patient was not correlated with visual acuity.

Macular Edema Following Retinal Vein Occlusion

On average, CPT reductions were observed in Studies RVO-1 and RVO-2 beginning at Day 7 following the first LUCENTIS injection through Month 6. CPT was not evaluated as a means to guide treatment decisions [*see Clinical Studies (14.2)*].

12.3 Pharmacokinetics

In animal studies, following intravitreal injection, ranibizumab was cleared from the vitreous with a half-life of approximately 3 days. After reaching a maximum at approximately 1 day, the serum concentration of ranibizumab declined in parallel with the vitreous concentration. In these animal studies, systemic exposure of ranibizumab is more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration, maximum ranibizumab serum concentrations were low (0.3 ng/mL to 2.36 ng/mL). These levels were below the concentration of ranibizumab (11 ng/mL to 27 ng/mL) thought to be necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 1 mg/eye. Serum ranibizumab concentrations in RVO patients were similar to those observed in neovascular AMD patients.

Based on a neovascular AMD population pharmacokinetic analysis, maximum serum concentrations of 1.5 ng/mL are predicted to be reached at approximately 1 day after monthly intravitreal administration of LUCENTIS 0.5 mg/eye. Based on the disappearance of ranibizumab from serum, the estimated average vitreous elimination half-life was approximately 9 days. Steady-state minimum concentration is predicted to be 0.22 ng/mL with a monthly dosing regimen. In humans, serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity data are available for ranibizumab injection in animals or humans.

No studies on the effects of ranibizumab on fertility have been conducted.

14 CLINICAL STUDIES

14.1 *Neovascular (Wet) Age-Related Macular Degeneration (AMD)*

The safety and efficacy of LUCENTIS were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1323 patients (LUCENTIS 879, Control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2

In Study AMD-1, patients with minimally classic or occult (without classic) CNV lesions received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly LUCENTIS 0.3 mg intravitreal injections and sham PDT; 2) monthly LUCENTIS 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham PDT (or active verteporfin PDT) was given with the initial LUCENTIS (or sham) intravitreal injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all LUCENTIS-treated patients (approximately 95%) maintained their visual acuity. 34%–40% of LUCENTIS-treated patients experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results. Detailed results are shown in the Table 3, Table 4, and Figure 1 below.

Table 3

Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n=238	LUCENTIS 0.5 mg n=240	Estimated Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	12	62%	95%	32% (26%, 39%)
	24	53%	90%	37% (29%, 44%)
Gain of ≥ 15 letters in visual acuity (%)[b]	12	5%	34%	29% (22%, 35%)
	24	4%	33%	29% (23%, 35%)
Mean change in visual acuity (letters) (SD)[b]	12	−10.5 (16.6)	+7.2 (14.4)	17.5 (14.8, 20.2)
	24	−14.9 (18.7)	+6.6 (16.5)	21.1 (18.1, 24.2)

[a] Adjusted estimate based on the stratified model.
[b] $p<0.01$.

Table 4

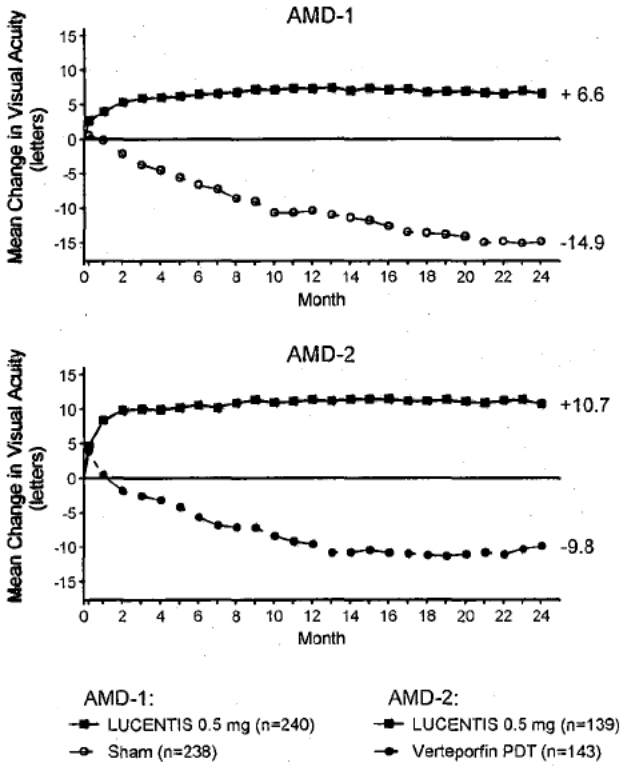
Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfin PDT n=143	LUCENTIS 0.5 mg n=139	Estimated Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	12	64%	96%	33% (25%, 41%)
	24	66%	90%	25% (16%, 34%)
Gain of ≥ 15 letters in visual acuity (%)[b]	12	6%	40%	35% (26%, 44%)
	24	6%	41%	35% (26%, 44%)
Mean change in visual acuity (letters) (SD)[b]	12	−9.5 (16.4)	+11.3 (14.6)	21.1 (17.5, 24.6)
	24	−9.8 (17.6)	+10.7 (16.5)	20.7 (16.8, 24.7)

[7] [a] Adjusted estimate based on the stratified model.
[b] $p<0.01$.

Figure 1

Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-1 and Study AMD-2

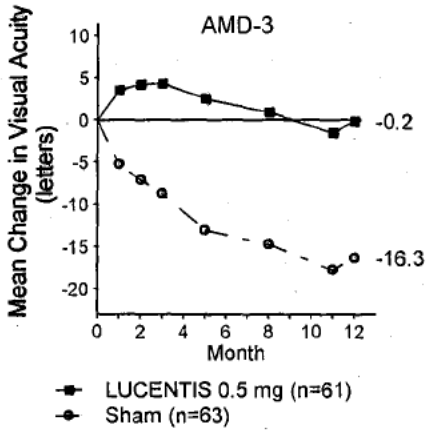


Patients in the group treated with LUCENTIS had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1–0.3 DA for LUCENTIS versus 2.3–2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3–0.4 DA for LUCENTIS versus 2.9–3.1 DA for the control arms.

Study AMD-3
Study AMD-3 was a randomized, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (LUCENTIS 0.3 mg, 60; LUCENTIS 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with LUCENTIS in Study AMD-3 received a mean of 6 total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 2). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with LUCENTIS lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all LUCENTIS-treated patients (90%) maintained their visual acuity at Month 12.

Figure 2
Mean Change in Visual Acuity from Baseline to Month 12 in Study AMD-3



14.2 Macular Edema Following Retinal Vein Occlusion (RVO)
The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, one-year studies in patients with macular edema following RVO. Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (LUCENTIS 0.3 mg, 266 patients; LUCENTIS 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. All patients completing Month 6 were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for rescue laser treatment beginning at Month 3 of the 6 month treatment period. Rescue laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg LUCENTIS and 72 of 132 (55%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

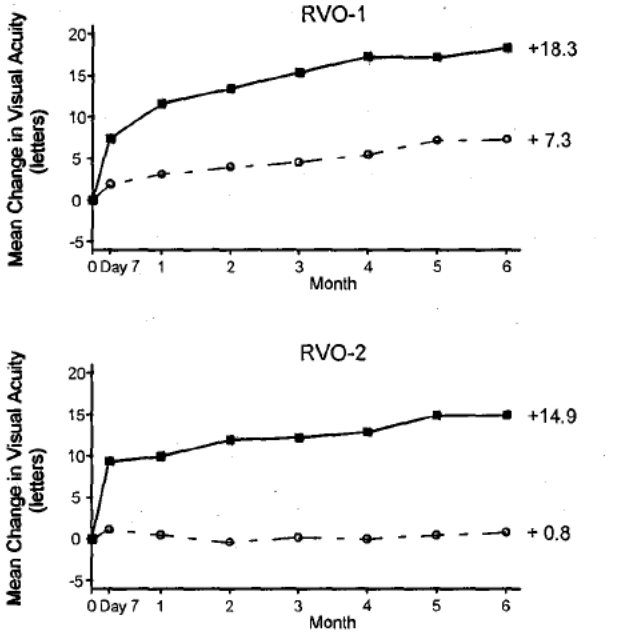
At Month 6, after monthly treatment with 0.5 mg LUCENTIS, the following clinical results were observed:

Table 5
Percentage of Patients with Gain of ≥15 letters in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2

Study	Sham	LUCENTIS 0.5 mg	Estimated Difference (95% CI)
RVO-1	29%	61%	31%[a] (20%, 43%)
RVO-2	17%	48%	30%[a] (20%, 41%)

[a] $p < 0.01$, adjusted estimate based on stratified model

Figure 3
Mean Change in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2



$p < 0.01$ for all time points

16 HOW SUPPLIED/STORAGE AND HANDLING
Each LUCENTIS carton, NDC 50242-080-01, contains a 0.2 mL fill of 10 mg/mL ranibizumab in a 2-cc glass vial; one 5-micron, 19-gauge × 1-1/2-inch filter needle for withdrawal of the vial contents; one 30-gauge × 1/2-inch injection needle for the intravitreal injection; and one package insert [*see Dosage and Administration (2.5)*]. VIALS ARE FOR SINGLE EYE USE ONLY.

LUCENTIS should be refrigerated at 2°–8°C (36°–46°F). DO NOT FREEZE. Do not use beyond the date stamped on the label. LUCENTIS

vials should be protected from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

LUCENTIS® [ranibizumab injection]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

4851401
Initial US Approval June 2006
Revision Date June 2010
LUCENTIS® is a registered trademark of Genentech, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

OFFICE DIRECTOR MEMO

Division Director Review for BLA 125156/S-053

Date	June 22, 2010
From	Wiley A. Chambers, M.D.
BLA #	125156
Applicant	Genentech, Inc.
Date of Submission	December 18, 2009
Type of Application	Supplement 053
Name	Lucentis (ranibizumab injection)
Dosage forms / Strength	Solution for intravitreal injection
Proposed New Indication(s)	For the treatment of patients with macular edema following retinal vein occlusion
Action:	Approval

1. Introduction

BLA 125156 for Lucentis (ranibizumab injection) was approved on June 30, 2006, for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) based on the review of Year-1 data from the two Phase 3 studies (FVF2587g and FVF2598g). The cumulative 2-year safety and efficacy data for both Phase 3 AMD studies are included in the current label. This supplemental BLA includes clinical information to support a revision of the package insert to include the new indication treatment of macular edema following retinal vein occlusion. The six month results are available from the following two studies:

- Study FVF4165g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Branch Retinal Vein Occlusion" (BRAVO)
- Study FVF4166g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion." (CRUISE)

2. CMC

From the Office of Biotechnology, Division of Monoclonal Antibodies, Memorandum of Review dated April 6, 2010: The ELISA assay, FBV.013, is acceptable for assessing formation of anti-ranibizumab antibodies in the retinal vein occlusion (RVO) subjects. A new assay, FBV.013, has been implemented for assessing formation of anti-drug antibodies in the retinal vein occlusion (RVO) subjects. The previous assays were submitted in the original BLA submission (Dec. 30, 2005) and amendment 17 in response to PMC 3 (Sept. 28, 2007; cross referenced from IND 8633). The ECLA assays developed in response to PMC3 use technology that is no longer available. The new assay, a bridging ELISA was validated in study FBV.013.AVR-0. The presence of antibodies in the initial bridging assay is confirmed by repeating the assay in the presence of an excess of unlabeled ranibizumab. Confirmed positives are characterized by titration. The Agency agreed that testing for neutralizing antibodies was not required if the anti-ranibizumab antibody rates were not higher in the RVO studies than in previous studies (July 23, 2009, pre-meeting package response).

3. Nonclinical Pharmacology/Toxicology

There is no new nonclinical pharmacology/toxicology data submitted in this supplement.

4. Clinical Pharmacology/Biopharmaceutics

There is no new clinical pharmacology/biopharmaceutics data submitted in this supplement.

5. Sterility Assurance

There is no new sterility assurance (product quality microbiology) data submitted in this supplement.

6. Clinical/Statistical - Efficacy

Study	Design (Sites)	Population	Control	Treatment Frequency and Duration	Ranibizumab Dose(s)
FVF4165g (BRAVO)	Randomized, double-masked, sham-controlled (US, Europe, Australia)	Subjects with macular edema following a branch vein occlusion	Sham injection	Intravitreal injection q month for 6 months followed by 6 month observation period in which PRN injections are permitted	0.3 mg (n=134), 0.5 mg (n=131), sham injection (n=132)
FVF4166g (CRUISE)	Randomized, double-masked, sham-controlled (US)	Subjects with macular edema following a central vein occlusion	Sham injection	Intravitreal injection q month for 6 months followed by a 6 month observation period in which PRN injections are permitted	0.3 mg (n=132), 0.5 mg (n=130), sham injection (n=130)
Study FVF3426g (HORIZON)	Extension study for patients previously enrolled in FVF4165g and FVF4166g	Retinal vein occlusions	None	PRN injections q month	0.5 mg

There were no significant problems identified Division of Scientific Investigations (DSI) audits that are likely to affect the data quality. The applicant has adequately disclosed financial arrangements with clinical investigators. There is no evidence suggesting problems with the integrity of the submitted data.

Study FVF4165g Primary Efficacy Results

Mean Change from Baseline in Visual Acuity in the Study Eye at Month 6 (ITT LOCF)

Visual Acuity at Month 6	Sham n=132	Ranibizumab	
		0.3 mg n=134	0.5 mg n=131
Number of letters change from baseline			
Mean (SD)	7.3 (13)	16.6 (11)	18.3 (13)
95% CI for mean	(5, 9)	(15, 18)	(16, 21)
Difference in LS means (vs. sham)		9	11
95% CI of the difference		(7, 12)	(8, 14)
p-value (vs. sham)		<0.0001	<0.0001

The treatment group differences were statistically significant but less than the 15 letter difference accepted as clinical significance.

Gain of ≥ 15 Letters from Baseline in Visual Acuity in the Study Eye at Month 6

Gain of ≥ 15 Letters from Baseline	Sham (n=132)	Ranibizumab	
		0.3 mg (n=134)	0.5 mg (n=131)
Randomized Subjects LOCF (Worst Outcome Imputation)			
N	132	134	131
Responders	36 (27%)	73 (54%)	78 (59%)
95% CI of the %	(20%, 35%)	(46%, 63%)	(51%, 68%)
Difference in % (vs. Sham)		27%	32%
95% CI of the difference		(16%, 39%)	(21%, 44%)
Treatment difference – p-value vs sham		<0.0001	<0.0001
Per Protocol Subjects (Observed Data)			
N	109	111	106
Responders	33 (30%)	64 (58%)	69 (65%)
95% CI of the %	(22%, 39%)	(48%, 67%)	(56%, 74%)
Difference in % (vs. Sham)		27%	35%
95% CI of the difference		(15%, 40%)	(22%, 47%)
Treatment difference – p-value vs sham		<0.0001	<0.0001

The difference in percentage of patients who gain 15 letters of vision is supportive of the application. The magnitude of the difference (approximately 30%) is consistent between the two studies.

Loss of < 15 Letters from Baseline in the Study Eye at Month 6

Loss of < 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Randomized Subjects LOCF			
N	132	134	131
Responders	126 (95%)	134 (100%)	129 (98%)
95% CI of the %	(92%, 98%)	(97%, 100%)	(95%, 100%)
Difference in % (vs. Sham)		5%	3%
95% CI of the difference		(2%, 10%)	(-1%, 8%)
p value for treatment difference vs sham		0.014	0.28
Randomized Subjects (Observed Data)			
N	121	126	123
Responders	117 (97%)	126 (100%)	122 (99%)
95% CI of the %	(92%, 99%)	(97%, 100.0%)	(96%, 100%)
Difference in % (vs. Sham)		3%	2%
95% CI of the difference		(0.3%, 8%)	(-2%, 8%)
P value for treatment difference vs sham		0.056	0.21

Central Foveal Thickness in the Study Eye at Month 6 (Randomized Subjects)

Central Foveal Thickness at Month 6	Sham (n=132)	Ranibizumab	
		0.3 mg (n=134)	0.5 mg (n=131)
≤ 250 µm			
N (%)	60 (45%)	122 (91%)	111 (85%)
95% CI for the %	(37%, 54%)	(86%, 96%)	(79%, 91%)
Difference in % (vs. Sham)		46%	40%
95% CI of the difference		(36%, 55%)	(30%, 50%)
p-value (vs. Sham)		<0.0001	<0.0001
Change from baseline (µm)			
Mean (SD)	-158 (224)	-337 (224)	-345 (238)
95% CI for the mean	(-196.3, -119)	(-375.6, -299)	(-386.4, -304)
Difference in % (vs. Sham)		-148	-135
95% CI of the difference		(-184, -114)	(-173, -97)
p-value (vs. Sham)		<0.0001	<0.0001

The difference between each of the ranibizumab groups and the sham group is statistically significant but the correlation to visual function is not known.

Study FVF4166g

Primary Efficacy Analysis

Mean Change from Baseline in Visual Acuity in the Study Eye at Month 6 Randomized Subjects

Visual Acuity at Month 6	Sham n=130	Ranibizumab	
		0.3 mg n=132	0.5 mg n=130
Number of letters change from baseline			
Mean (SD)	1 (16)	13 (16)	15 (13)
95% CI for mean	(-2,4)	(10, 15)	(13, 17)
Difference in LS means (vs. sham)		11	14
95% CI of the difference		(8, 15)	(10, 17)
p-value (vs. sham)		<0.0001	<0.0001

The treatment group differences were statistically significant but less than the 15 letter difference accepted as clinically significant.

Gain of ≥ 15 Letters from Baseline in the Study Eye at Month 6

Gain of ≥ 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Randomized Subjects LOCF (Worst Outcome Imputation)			
N	130	132	130
Responders	21 (16%)	57 (43%)	56 (43%)
95% CI of the %	(10%, 22%)	(35%, 52%)	(35%, 52%)
Difference in % (vs. Sham)		27%	27%
95% CI of the difference		(16%, 38%)	(16%, 37%)
p-value (vs. Sham)		<0.0001	<0.0001
Per Protocol Subjects (Observed Data)			
N	104	118	102
Responders	21 (20%)	56 (47%)	53 (52%)
95% CI of the %	(12%, 28%)	(38%, 56%)	(42%, 62%)
Difference in % (vs. Sham)		27%	32%
95% CI of the difference		(15%, 39%)	(19%, 44%)
p-value (vs. Sham)		<0.0001	<0.0001

The difference in percentage of patients who gain 15 letters of vision is supportive of the application. The magnitude of the difference (approximately 30%) is consistent between the two studies.

Loss of < 15 Letters from Baseline in the Study Eye at Month 6

Loss of < 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Randomized Subjects LOCF (Worst Outcome Imputation)			
N	130	132	130
Responders	97 (75%)	118 (90%)	109 (84%)
95% CI of the % [a]	(67%, 82%)	(84%, 95%)	(77%, 90%)
Difference (CI) in % (vs. Sham) [b]		15% (6%, 24%)	9% (-1%, 19%)
p-value (vs. Sham) [c]		0.002	0.065
Per Protocol Subjects (Observed Data)			
N	104	118	102
Responders	91 (88%)	113 (96%)	100 (98%)
95% CI of the % [a]	(81%, 94%)	(92.1%, 99%)	(95.3%, 100%)
Difference in % (vs. Sham) [b]		8% (1%, 16%)	10% (4%, 17%)
p-value (vs. Sham) [c]		0.03	0.005

Central Foveal Thickness in the Study Eye at Month 6 (Randomized Subjects)

Central Foveal Thickness at Month 6	Sham (n=130)	Ranibizumab	
		0.3 mg (n=132)	0.5 mg (n=130)
≤ 250 µm			
n (%)	30 (23.1%)	99 (75%)	100 (77%)
95% CI for the %	(15.8%, 30.3%)	(68%, 82%)	(70%, 84%)
Difference in % (vs. Sham)		52% (42%, 62%)	54% (44%, 64%)
p-value (vs. Sham)		<0.0001	<0.0001
Change from baseline (µm)			
N	129	131	130
Mean (SD)	-168 (308)	-433.7 (296)	-452.3 (258)
95% CI for the mean	(-222, -114)	(-485, -383)	(-497, -408)
Difference in % (vs. Sham)		-272 (-330, -215)	-284 (-338, -230)
p-value (vs. Sham)		<0.0001	<0.0001

The central foveal thickness differences are statistically significant, but the correlation to visual function is not known.

The statistical analyses were conducted according to the statistical analysis plan. The Statistical reviewer found the Applicant's analyses of the primary efficacy endpoint acceptable. The statistical reviewer also conducted additional analyses to examine the robustness of the results from the Applicant's analysis. The results from these analyses are consistent with those from the Applicant's analysis.

Efficacy Summary Statement

The 6-Month Clinical Study Reports submitted within this Supplemental BLA 125156 for Study FVF4165g and Study FVF4166g support the efficacy of ranibizumab 0.5 mg injection in the treatment of the macular edema following retinal vein occlusion. The two Phase 3 studies demonstrate replicative results in the ability of ranibizumab to improve vision in patients with macular edema following retinal vein occlusion when given intravitreally every four weeks (approximately every 28 days) when compared to sham treatment.

At Month 6, patients entered into a continued observation period. Treatments between months 6-11 were based on OCT findings of the macular thickness and visual acuity (PRN treatment). Approximately 50% of patients received treatment with Lucentis at month 6. The vast majority of patients who did not receive treatment, had a decrease in visual acuity. Genentech has agreed to study the effect of continued treatment when the OCT and visual acuity findings might suggest that no further treatment is necessary.

(b) (4) the National Eye Institute – Visual Function Quality Test – 25 which was a secondary efficacy outcome as a patient reported outcome (b) (4) The instrument does not appear to have been externally validated and does not demonstrate a convincingly clinically relevant change in patient response from baseline to Month 6. (b) (4)

7. Safety

This review of safety describes the safety profile of Lucentis (ranibizumab injection) for the treatment of macular edema following retinal vein occlusion (RVO). Data from Studies FVF4165g and FVF4166g, two Phase 3 studies in RVO, are included in this section.

SIGNIFICANT ADVERSE EVENTS

Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the 6-Month Treatment Period: Studies FVF4165g and FVF4166g (Safety Evaluable Subjects)

MedDRA Preferred Term	Study FVF4165g			Study FVF4166g		
	Sham n=131	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=130	Sham N=129	Ranibizumab 0.3 mg n=132	Ranibizumab 0.5 mg n=129
Any adverse event	**1 (0.8%)**	**4 (3.0%)**	**5 (3.8%)**	**2 (1.6%)**	**2 (1.5%)**	**2 (1.6%)**
Arterial thromboembolic events						
Any adverse event	1	0	3	1	2	2
Acute coronary syndrome	0	0	0	1	0	0
Acute myocardial infarction	0	0	1	0	1	1
Angina pectoris	0	0	0	0	0	1
Angina unstable	0	0	1	0	0	0
Cerebral hemorrhage	0	0	1	0	0	0
Retinal artery occlusion	0	0	0	0	1	0
Thalamus hemorrhage	1	0	0	0	0	0
Transient ischemic attack	0	0	0	0	0	1
Hypertension						
Any adverse event	0	2	0	1	0	0
Hypertension	0	2	0	1	0	0
Non-ocular hemorrhage						
Any adverse event	1	2	2	0	0	0
Cerebral hemorrhage	0	0	1	0	0	0
Intra-abdominal hematoma	0	1	0	0	0	0
Post procedural hemorrhage	0	0	1	0	0	0
Rectal hemorrhage	0	1	0	0	0	0
Thalamus hemorrhage	1	0	0	0	0	0
Other potentially associated						

MedDRA Preferred Term	Study FVF4165g			Study FVF4166g		
	Sham n=131	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=130	Sham N=129	Ranibizumab 0.3 mg n=132	Ranibizumab 0.5 mg n=129
events						
Any adverse event	0	0	1	0	0	0
Intestinal perforation	0	0	1	0	0	0

Note: Table counts include subjects with at least one adverse event of the type specified.

Serious adverse events potentially related to systemic VEGF inhibition during the 6 month treatment period occurred at a rate of 1-4% in the ranibizumab-treated groups. In Study FVF4165g, there were more events in the ranibizumab-treated groups. In Study FVF4166g, the numbers of events were evenly distributed across all treatment groups.

APTC Arterial Thromboembolic Events during the 6-Month Treatment Period: Studies FVF4165g and FVF4166g (Safety Evaluable Subjects)

Type of Adverse Event	Study FVF4165g			Study FVF4166g		
	Sham n=131	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=130	Sham n=129	Ranibizumab 0.3 mg n=132	Ranibizumab 0.5 mg N=129
Any event	**1 (0.8%)**	**0**	**2 (1.5%)**	**1 (0.8%)**	**1 (0.8%)**	**1 (0.8%)**
Nonfatal myocardial infarction	0	0	1	1	1	1
Fatal cerebrovascular accident	0	0	1	0	0	0
Nonfatal cerebrovascular accident	1	0	0	0	0	0
Vascular death	0	0	1	0	0	0
APTC event (vascular death, unknown cause death, non-fatal myocardial infarction, non-fatal cerebrovascular accident)	1	0	2	1	1	1

Applying the Antiplatelet Trialists' Collaboration (APTC) classification to the serious adverse events, the overall frequency of events is less than 2% and similar across all treatment groups in both studies.

COMMON ADVERSE EVENTS

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

Adverse Events Occurring in ≥ 1 % of Patients during the 6-Month Treatment Period: Studies FVF4165g and Study FVF4166g Pooled Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Sham N=260	Ranibizumab Pooled	
		0.3 mg N=266	0.5 mg N=259
Blood and Lymphatic System Disorders			
Anemia	3 (1.2%)	3 (1.1%)	3 (1.2%)
Cardiac Disorders			
Coronary artery disease	3 (1.2%)	1 (0.4%)	2 (0.8%)
Ear and Labyrinth Disorders			
Vertigo	7 (2.7%)	3 (1.1%)	1 (0.4%)
Eye Disorders			
Blepharitis	3 (1.2%)	3 (1.1%)	1 (0.4%)
Cataract	4 (1.5%)	3 (1.2%)	6 (2.3%)
Conjunctival hemorrhage	97 (37.3%)	137 (51.5%)	124 (47.9%)
Conjunctival hyperemia	1 (0.4%)	4 (1.5%)	1 (0.4%)
Conjunctivitis	0	0	3 (1.2%)
Corneal abrasion	4 (1.5%)	4 (1.5%)	1 (0.4%)
Diplopia	1(0.4%)	4 (1.5%)	2 (0.8%)
Drug administration error	4 (1.5%)	2 (0.8%)	1 (0.4%)
Dry Eye	7 (2.7%)	6 (2.3%)	7 (2.7%)
Eye discharge	3 (1.2%)	3 (1.1%)	6 (2.3%)
Eye irritation	16 (6.2%)	14 (5.3%)	17 (6.6%)
Eye pain	32 (12.3%)	44 (16.5%)	45 (17.4%)
Eye pruritus	6 (2.3%)	7 (2.6%)	3 (1.2%)
Eyelid edema	4 (1.5%)	2 (0.8%)	2 (0.8%)
Foreign body sensation in eyes	13 (5.0%)	10 (3.8%)	18 (6.9%)
Intraocular pressure increased	6 (2.3%)	18 (6.8%)	17 (6.6%)
Iris neovascularization	12 (4.6%)	2 (0.8%)	1 (0.4%)
Iritis	7 (2.7%)	3 (1.1%)	2 (0.8%)
Keratitis	0	1 (0.4%)	3 (1.2%)
Lacrimation increased	7 (2.7%)	10 (3.8%)	5 (1.9%)
Macular edema	16 (6.2%)	9 (3.4%)	5 (1.9%)
Macular ischemia	3 (1.2%)	0	0
Maculopathy	19 (7.3%)	36 (13.5%)	28 (10.8%)
Metamorphopsia	3 (1.2%)	5 (1.9%)	3 (1.2%)
Ocular discomfort	6 (2.3%)	3 (1.1%)	6 (2.3%)
Ocular hyperemia	7 (2.7%)	18 (6.8%)	13 (5.0%)
Optic atrophy	1 (0.4%)	0	4 (1.5%)
Optic disc vascular disorder	8 (3.1%)	13 (4.9%)	2 (0.8%)
Ocular vascular disorder	13 (5.0%)	17 (6.4%)	17 (6.6%)
Papilledema	5 (1.9%)	3 (1.1%)	2 (0.8%)
Photopsia	3 (1.2%)	4 (1.5%)	4 (1.5%)
Punctate keratitis	2 (0.8%)	5 (1.9%)	4 (1.5%)
Retinal depigmentation	11 (4.2%)	17 (6.4%)	23 (8.9%)

MedDRA System Organ Class Preferred Term	Sham N=260	Ranibizumab Pooled	
		0.3 mg N=266	0.5 mg N=259
Retinal disorder	3 (1.2%)	3 (1.1%)	6 (2.3%)
Retinal exudates	33 (12.7%)	69 (25.9%)	54 (20.8%)
Retinal hemorrhage	29 (11.2%)	32 (12.0%)	29 (11.2%)
Retinal neovascularization	8 (3.1%)	2 (0.8%)	2 (0.8%)
Retinal pigmentation	9 (3.5%)	8 (3.0%)	6 (2.3%)
Retinal vascular disorder	24 (9.2%)	30 (11.3%)	32 (12.4%)
Retinal vein occlusion	3 (1.2%)	2 (0.8%)	1 (0.4%)
Vision blurred	8 (3.1%)	9 (3.4%)	12 (4.6%)
Visual acuity reduced	3 (1.2%)	0	3 (1.2%)
Visual impairment	3 (1.2%)	6 (2.3%)	2 (0.8%)
Vitreous detachment	6 (2.3%)	7 (2.6%)	10 (3.9%)
Vitreous floaters (Myodesopsia)	6 (2.3%)	26 (9.8%)	18 (6.9%)
Vitreous hemorrhage	15 (5.8%)	11 (4.5%)	9 (3.5%)
Gastrointestinal Disorders			
Diarrhea	7 (2.7%)	5 (1.9%)	1 (0.4%)
Dyspepsia	4 (1.5%)	0	1 (0.4%)
Gastroesophageal reflux disease	1 (0.4%)	3 (1.1%)	2 (0.8%)
Nausea	4 (1.5%)	2 (0.8%)	3 (1.2%)
Toothache	3 (1.2%)	2 (0.8%)	2 (0.8%)
Vomiting	4 (1.5%)	1 (0.4%)	3 (1.2%)
General Disorders and Administration Site Conditions			
Edema peripheral	3 (1.2%)	2 (0.8%)	1 (0.4%)
Pain	2 (0.8%)	3 (1.1%)	2 (0.8%)
Immune System Disorders			
Hypersensitivity	1 (0.4%)	2 (0.8%)	4 (1.5%)
Seasonal allergy	5 (1.9%)	4 (1.5%)	1 (0.4%)
Infections and Infestations			
Bronchitis	4 (1.5%)	3 (1.1%)	1 (0.4%)
Cystitis	1 (0.4%)	1 (0.4%)	3 (1.2%)
Influenza	5 (1.9%)	4 (1.5%)	8 (3.1%)
Nasopharyngitis	10 (3.8%)	14 (5.3%)	14 (5.4%)
Pneumonia	4 (1.5%)	4 (1.5%)	1 (0.4%)
Sinusitis	5 (1.9%)	14 (5.3%)	8 (3.1%)
Upper respiratory tract infection	4 (1.5%)	7 (2.6%)	6 (2.3%)
Urinary tract infection	4 (1.5%)	5 (1.9%)	2 (0.8%)
Injury, Poisoning and Procedural Complications Contrast Media Reaction			
Contusion	5 (1.9%)	2 (0.8%)	4 (1.5%)
Fall	6 (2.3%)	2 (0.8%)	5 (1.9%)
Upper limb fracture	0	3 (1.1%)	0
Investigations			
Blood pressure increased	2 (0.8%)	2 (0.8%)	3 (1.2%)
Metabolism and Nutrition Disorders			
Hypercholoesterolemia	3 (1.2%)	4 (1.5%)	2 (0.8%)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	2 (0.8%)	3 (1.1%)	6 (2.3%)
Arthritis	1 (0.4%)	3 (1.1%)	2 (0.8%)
Back pain	2 (0.8%)	4 (1.5%)	7 (2.7%)

MedDRA System Organ Class Preferred Term	Sham N=260	Ranibizumab Pooled	
		0.3 mg N=266	0.5 mg N=259
Muscle spasms	4 (1.5%)	0	2 (0.8%)
Neck pain	1 (0.4%)	3 (1.1%)	0
Osteoarthritis	1 (0.4%)	4 (1.5%)	0
Osteoporosis	1 (0.4%)	0	3 (1.2%)
Pain in extremity	2 (0.8%)	3 (1.1%)	2 (0.8%)
Nervous System Disorders			
Dizziness	9 (3.5%)	6 (2.3%)	2 (0.8%)
Headache	9 (3.5%)	13 (4.9%)	7 (2.7%)
Sinus headache	1 (0.4%)	0	3 (1.2%)
Psychiatric Disorders			
Anxiety	4 (1.5%)	4 (1.5%)	2 (0.8%)
Depression	1 (0.4%)	2 (0.8%)	3 (1.2%)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	4 (1.5%)	3 (1.1%)	4 (1.5%)
Nasal congestion	4 (1.5%)	1 (0.4%)	0
Sinus congestion	1 (0.4%)	2 (0.8%)	4 (1.5%)
Skin and Subcutaneous Disorders			
Hyperhidrosis	0	0	3 (1.2%)
Rash	3 (1.2%)	2 (0.8%)	2 (0.8%)
Vascular Disorders			
Hypertension	21 (8.1%)	16 (6.0%)	13 (5.0%)

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

Many of these adverse events are commonly associated with the condition treated, as well as, conjunctival anesthetic and intravitreal injection procedures.

LABORATORY FINDINGS/IMMUNOGENICITY

During the 6-month treatment period, serum samples for the evaluation of antibodies to ranibizumab were obtained at screening (baseline) and at Month 6, prior to study drug administration. Of the subjects with evaluable samples at baseline, 3.5%, 2.7%, and 3.2% of subjects in the sham, 0.3-mg, and 0.5-mg groups, respectively, tested positive for antibodies to ranibizumab, possibly due to preexisting anti-Fab antibodies[1]. At Month 6, 3.6%, 1.7%, and 2.7% of subjects with evaluable samples in the sham, 0.3-mg, and 0.5-mg groups, respectively, tested positive for antibodies to ranibizumab.

Adverse events and visual acuity outcomes for subjects who tested positive for antibodies to ranibizumab at any timepoint during the 6-month treatment period were reviewed. Changes in visual acuity from baseline to Month 6 were consistent with the larger study population. When subjects with and without positive antibody responses were compared, no clinically significant differences in adverse events were found.

[1] Süsal C, Döhler B, Opelz G. Graft-protective role of high pretransplantation IgA-anti-Fab autoantibodies: confirmatory evidence obtained in more than 4000 kidney transplants. The Collaborative Transplant Study. Transplantation. 2000 Apr 15;69(7):1337-40

Antibodies to Ranibizumab during the 6-Month Treatment Period

Timepoint	No. of Subjects Who Tested Positive for Antibodies / No. of Subjects with Evaluable Samples (%)		
	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Baseline	6/129 (4.7%)	1/129 (0.8%)	5/127 (3.9%)
Month 6	4/112 (3.6%)	2/117 (1.7%)	3/112 (2.7%)

Antibodies to Ranibizumab at Month 6 by Baseline Antibody Status

Timepoint	No. of Subjects Who Tested Positive for Antibodies at Month 6 / No. of Subjects with Specified Baseline Status Who Were Tested at Month 6		
	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Positive	4/4	1/1	2/2
Negative	0/107	1/112	1/110
Missing	0/1	0/4	0/0

8. Advisory Committee Meeting

No Advisory Committee Meeting was considered necessary for this Lucentis (ranibizumab injection) supplement.

9. Pediatrics

The population studied for this indication was predominantly in the 7th and 8th decades of life reflective of the population most affected by this disease. The demographics of the patients enrolled in the trial during the development program for this proposed indication are representative of the targeted population.

The applicant requested and received a waiver of the pediatric study requirements for the original Biologics License Application. In its written pre-submission advice for this supplement, the FDA agreed to Genentech's request for a Pediatric Waiver. The waiver was requested because the disease under study (macular edema following retinal vein occlusion) rarely occurs in the pediatric age group.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Regulatory Action

Lucentis (ranibizumab injection) with the labeling changes listed in this review is to be approved for the additional indication of treatment of patients with macular edema following retinal vein occlusion.

The applicant, Genentech Inc. has conducted two adequate and well-controlled studies, FVF25g, and FVF25g which demonstrated statistically and clinically significant differences in the proportion of subjects who gain more than 15 letters in best corrected vision at 6 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.

Postmarketing Commitments (PMC)

Genentech has committed to conduct a Phase 4 study which provides safety and efficacy data on at least 150 patients with macular edema following a retinal vein occlusion, followed for at least 15 months and randomized sometime within 15 months of their first treatment with Lucentis. Patients must receive 7 monthly doses of Lucentis, be evaluated monthly for the need of additional doses of Lucentis based on OCT and visual acuity criteria and if determined to not need an additional monthly dose of Lucentis be randomized to receive an additional dose or not to receive an additional dose of Lucentis.

- Protocol submitted to FDA: November 1, 2010
- Study Start (FPI): March 1, 2011
- CSR Submission: October 1, 2013

Genentech will also provide the full study reports from the 6 month observation periods for Study FVF4165g and FVF4166g and the full study report for Study FVF3426g. Genentech will submit the clinical study reports to address these two PMC proposals by October 1, 2010 and 1 November, 2011, respectively.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA 125156
Submission Number	053
Submission Code	Supplement
Letter Date	December 18, 2009
Stamp Date	December 21, 2009
PDUFA Goal Date	June 22, 2010
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	May 18, 2010
Established Name	ranibizumab injection
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	P

Formulation

Ingredients	Strength Amount per 10 mg/mL Vial [a]	Function	Reference to Standard or Specification
Ranibizumab	(b) (4)	Active ingredient	
α, α-trehalose dehydrate		(b) (4)	
(b) (4) histidine HCl			Ph. Eur.
(b) (4)			USP and Ph. Eur.
(b) (4)			NF and Ph. Eur.
Polysorbate 20			USP and Ph. Eur.
Water for Injection			

Dosing Regimen
Lucentis 0.5 mg (0.05 mL) is to be administered by intravitreal injection once a month (approximately 28 days).

Indication
For the treatment of patients with macular edema following retinal vein occlusion.

Intended Population
Adults with macular edema secondary to retinal vein occlusion.

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Supplement (S-053) for BLA 125156 Lucentis (ranibizumab injection) is recommended for approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.2.2 Required Phase 4 Commitments

Genentech commits to the following postmarketing commitments:

1. Submit the clinical study reports (CSRs) from the 6 month observation periods for Study FVF4165g and FVF4166g by October 1, 2010.

2. Submit the CSR from Study FVF3426g by November 1, 2011.

3. Provide safety and efficacy data on at least 150 patients with macular edema following a retinal vein occlusion, followed for at least 15 months and randomized sometime within 15 months of their first treatment with Lucentis. Patients must receive 7 monthly doses of Lucentis, be evaluated monthly for the need of additional doses of Lucentis based on OCT and visual acuity criteria and if determined to not need an additional monthly dose of Lucentis be randomized to receive an additional dose or not to receive an additional dose of Lucentis.

    - Protocol submitted to FDA: November 1, 2010
    - Study Start (First Patient In): March 1, 2011
    - CSR Submission: October 1, 2013

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
Trade Name	Lucentis
Therapeutic Class	vascular endothelial growth factor (VEGF) inhibitor
Route of Administration	intravitreal injection

Reference is made to BLA 125156 for Lucentis (ranibizumab injection) approved on June 30, 2006, for the treatment of patients with neovascular (wet) age-related macular degeneration based on the review of Year-1 data from the two Phase 3 studies (FVF2587g and FVF2598g). The cumulative 2-year safety and efficacy data for both Phase 3 AMD studies are included in the current label.

In this supplemental BLA, Genentech seeks to update the ranibizumab label with a new indication, the treatment of macular edema following retinal vein occlusion (RVO).

1.3.2 Efficacy

This supplemental BLA includes clinical information to support revision of the Lucentis U.S. Package Insert to include the new indication treatment of macular edema following retinal vein occlusion. The six month results from the following two studies:

- Study FVF4165g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Branch Retinal Vein Occlusion"
- Study FVF4166g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion"

1.3.3 Safety

Supported by efficacy studies listed in Section 1.3.2.

1.3.4 Dosing Regimen and Administration

Lucentis (ranibizumab injection) 0.5 mg (0.05 mL) is administered by intravitreal injection once a month (approximately 28 days).

1.3.5 Drug-Drug Interactions

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.

The population studied for this indication was predominantly in the 7th and 8th decades of life reflective of the population most affected by this disease. The demographics of the patients enrolled in the trial during the development program for this proposed indication are representative of the targeted population. No additional data are needed from other populations. The number of patients outside of this demographic group was too small to draw definitive conclusions regarding safety and efficacy. There do not appear to have been any race or ethnicity effects.

Retinal vein occlusion is a disease seen only in adults; therefore, no pediatric trials were conducted for this drug.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

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

Reference is made to BLA 125156 for Lucentis (ranibizumab injection) approved on June 30, 2006, for the treatment of patients with neovascular (wet) age-related macular degeneration based on the review of Year-1 data from the two Phase 3 studies (FVF2587g and FVF2598g) during the original review cycle. The cumulative 2-year safety and efficacy data for both Phase 3 AMD studies are included in the current label.

In this supplemental BLA, Genentech seeks to update the ranibizumab label with a new indication, the treatment of macular edema following retinal vein occlusion.

2.2 Currently Available Treatment for Indications

Ozurdex (dexamethasone intravitreal implant) was approved for the treatment of macular edema following branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) on June 19, 2009.

2.3 Availability of Proposed Active Ingredient in the United States

Ranibizumab injection is currently marketed by the applicant as Lucentis (ranibizumab injection) for the treatment of neovascular (wet) age-related macular degeneration.

2.4 Important Issues With Pharmacologically Related Products

There have been no additional safety concerns raised with this class of therapeutic products other than those listed in the current Lucentis (ranibizumab injection) package insert and those discussed within this review.

2.5 Presubmission Regulatory Activity

On 29 January 2007, a Type C meeting was held regarding preliminary protocol concepts for a clinical development plan for ranibizumab for treatment of patients with macular edema secondary to RVO. Following the submission of protocols for Studies FVF4165g and FVF4166g, in a letter dated 29 June 2007, FDA forwarded additional written comments regarding the protocols.

In a letter dated October 18, 2007, Genentech indicated that some of the FDA requested changes would be incorporated in the protocols. The FDA recommendation against the use of sham injection as the primary control and suggestion to use at least three doses in the studies to demonstrate dose response and ensure adequate masking were not incorporated into the protocols. At the time that the studies were initiated, Genentech did not consider the benefits and risks of including ranibizumab doses either higher or lower than 0.3 mg and 0.5 mg appropriate.

[redacted] (b) (4)

On July 6, 2009, Genentech received draft written advice for a planned Type B meeting, scheduled for 13 July 2009, to discuss Genentech's plans to submit a sBLA for ranibizumab for the treatment of patients with macular edema secondary to RVO.

In its written pre-submission advice, the FDA agreed to Genentech's request for a Pediatric Waiver.

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 supplental BLA does not contain any Chemistry, Manufacturing and Controls information or changes.

3.2 Animal Pharmacology/Toxicology

This supplemental BLA does not contain any Animal Pharmacology/Toxicology information or changes.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on the information submitted by the applicant in support of updating the ranibizumab label. This supplemental BLA includes clinical information to support revision of the Lucentis U.S. Package Insert to include the new indication treatment of macular edema following retinal vein occlusion. The six month results from the following two studies:

- Study FVF4165g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Branch Retinal Vein Occlusion"
- Study FVF4166g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion"

This supplemental BLA 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

This supplemental BLA contains the clinical study reports of the 6 month results of Study FVF4165g and FVF4166g.

Study	Phase	Design (Sites)	Population	Control	No. of Enrolled Subjects	Treatment Frequency and Duration	Ranibizumab Dose(s)	Status
FVF4165g (BRAVO)	3	Randomized, double-masked, sham -controlled (US)	Subjects with macular edema secondary to BRVO	Sham injection for 6-month treatment period	397	Intravitreal injection q month during 6-month treatment period, followed by a 6month observation period with retreatments q month, prn according to protocol specified criteria (Max. 12 injxns over 1 yr)	0.3 mg (n=134), 0.5 mg (n=131), sham injection (n=132)	Observation period ongoing
FVF4166g (CRUISE)	3	Randomized, double-masked, sham-controlled (US)	Subjects with macular edema secondary to CRVO		392		0.3 mg (n=132), 0.5 mg (n=130), sham injection (n-130)	Observation period ongoing
FVF3426g (HORIZON)	Extension	Open-label, multicenter extension study (US)	Cohort 2: Subjects with macular edema secondary to RVO who have completed Study FVF4166g or FVF4165g`	None	Up to 739[a] in Cohort 2	Cohort 2: Intravitreal Injxns no more frequently than every 30 days for up to 2 years or until 30 days after FDA approval	0.5 mg (n= up to 730 in Cohort 2)	Ongoing

a Because enrollment is ongoing, the number of subjects is the planned enrollment approximated on the basis of the total number of subjects who completed Study FVF4165g or Study FVF4166g through Month 6.

4.3 Review Strategy

This review evaluates the 6 month results for the two Phase 3 clinical trials FVF4165g and FVF4166g.

4.4 Data Quality and Integrity

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

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's 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 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

The pharmacology of ranibizumab was well described in the original BLA submission for the treatment of neovascular (wet) AMD. Although clinical pharmacology studies were not performed in retinal vein occlusion patients, pharmacokinetic and pharmacodynamic data were obtained in studies FVF4165g and FVF4166g.

5.1 Pharmacokinetics

Ranibizumab is administered as an intravitreal injection, with the site of action in the retina. Following administration, ranibizumab is absorbed into the systemic circulation, where it can be measured in serum. Systemic ranibizumab pharmacokinetics had been previously well described

in AMD patients using a population pharmacokinetic approach, and results of these analyses were submitted in the AMD BLA (STN: BL 125156). Analysis of the RVO data addressed two objectives. The first objective was to assess the similarity of observed systemic concentrations in RVO patients relative to those in AMD patients, given that the two diseases share pathophysiologic characteristics. Subsequent analyses were conducted to evaluate potential dose-adjustment requirements for RVO patients.

Observed ranibizumab concentrations were similar at post-dose timepoints common in the RVO and AMD studies. Additionally, simulations with the one-compartment model developed for AMD were able to describe the ranibizumab systemic exposure in RVO patients well. Together, these analyses demonstrated that systemic ranibizumab concentrations were similar in RVO and AMD patients and that the AMD structural model was appropriate for further analyses of the RVO data.

No clinically meaningful effects requiring dose adjustment were identified in the RVO covariate analysis. The effect of renal function (as measured by creatinine clearance) on systemic clearance was the only statistically significant effect identified. However, observed and predicted concentrations for RVO subjects with a range of creatinine clearance values were entirely below the concentration thought to be necessary to inhibit the biologic activity of VEGF-A by 50%. Therefore, the effects of renal insufficiency on systemic exposure were not considered clinically meaningful. Overall, no dose adjustment is necessary when considering treatment of RVO patients.

5.2 Pharmacodynamics

The production of VEGF in the retina following RVO is believed to contribute to macular edema. Retinal thickness measured as central foveal thickness (CFT; also referred to as center point thickness) with optical coherence tomography (OCT) provides a valuable morphologic assessment reflecting the biologic activity of ranibizumab. The magnitude and time course of the biologic effect of ranibizumab were assessed in Studies FVF4165g and FVF4166g through measurements at baseline, on Day 7, and throughout the study.

In both studies, the difference between each of the ranibizumab groups and the sham injection group in the proportion of subjects with a CFT of ≤ 250 μm at 6 months was measured. The proportion of subjects achieving a CFT of ≤ 250 μm was greater with ranibizumab treatment than with sham injection. The results were both clinically meaningful and statistically significant ($p < 0.0001$) for both ranibizumab treatment groups in both studies.

Statistically significant and clinically meaningful differences in mean change from baseline in CFT for ranibizumab-treated versus sham control subjects were evident early after treatment initiation, 7 days after the first dose. The mean CFT decreases were sustained with monthly dosing and remained statistically significant compared with sham injections at all timepoints for which OCT images were graded by the central reading center (Day 7, Months 1–3, and Month 6).

5.3 Exposure-Response Relationships

The retina is the site of disease in macular edema following retinal vein occlusion. Therefore, systemic ranibizumab concentrations after intravitreal administration are not expected to correlate with efficacy.

The systemic pharmacokinetics of ranibizumab were characterized throughout the clinical program, including a population pharmacokinetic analysis.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This supplemental BLA presents information to support revison of the Lucentis package insert for the treatment of macular edema following retinal vein occlusion (RVO).

Lucentis (ranibizumab injection) was approved for the treatment of patients with neovascular (wet) age-related macular degeneration on June 30, 2006.

6.1.1 Methods

The 6-month data from Phase 3 studies FVF4165g and FVF4166g are submitted in this supplemental BLA which will be reviewed for safety and efficacy. The efficacy review is based on the Phase 3 studies submitted in this application:

- Study FVF4165g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Branch Retinal Vein Occlusion"
- Study FVF4166g, "A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion"

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 macular edema and AMD.

(b) (4) (b) (4) the National Eye Institute – Visual Function Quality Test – 25 which was a secondary efficacy outcome as a patient reported outcome (b) (4) At the pre-sBLA meeting held with the Division, the reommendation was

given to the applicant to address the deficiencies noted in the prior sBLA (BL125156/S-011) (b) (4) (b) (4) In fulfillment of this recommendation, the applicant has submitted the following information:

- Evidence Dossier (b) (4) Patient-Reported Visual Function Outcomes (b) (4) (b) (4)
- Content Validation of the NEI VFQ-25 in Retinal Vein Occlusion

The Division obtained a consult from the Study Endpoint and Labeling Development (SEALD) review team in order to adequately evaluate this submitted data. Following is the Executive Summary from the SEALD review:

> "This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Anti-Infective and Ophthalmology Products regarding BLA 125156/S053 for Lucentis (ranibizumab injection). The sponsor submitted an efficacy supplement to support an indication for the treatment of macular edema following retinal vein occlusion.
>
> (b) (4)
>
> (b) (4)

Reviewer's Comment:

The Division has independently reviewed the submitted data in (b) (4)

(b) (4)

(b) (4) (b) (4)

6.1.3 Study Design

The clinical development plan for the retinal vein occlusion indication included two Phase 3 studies, FVF4165g and FVF4166g, included in this Supplement. Both studies are ongoing, randomized, multicenter, double masked, sham injection-controlled trials with primary efficacy endpoint measured at 6 months. Other than the subtype of retinal vein occlusion enrolled, the trials have essentially the same inclusion and exclusion criteria. Additionally, the overall study designs of the trials are similar in terms of treatment schedule, study assessments, and primary and secondary efficacy endpoints.

One major difference between the two is that Study FVF4165g provides laser photocoagulation as rescue treatment in all treatment groups, beginning at Month 3. Study FVF4166g does not offer rescue treatment.

6.1.3.1 **Study FVF4165g**: A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Branch Retinal Vein Occlusion

Primary Objectives:

- To evaluate the efficacy of intravitreal injections of ranibizumab administered monthly for 6 months in the improvement of visual acuity as measured by the mean change in best corrected visual acuity (BCVA) at 6 months compared with baseline
- To evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly for 6 months, followed by a 6-month observation period with protocol-specified retreatment criteria

Secondary Objectives:

- To evaluate the efficacy of intravitreal injections of ranibizumab administered monthly for 6 months with respect to visual acuity outcomes (other than mean change in BCVA score at 6 months compared with baseline), anatomic outcomes, and patient-reported visual function outcomes
- To evaluate the pharmacokinetics of ranibizumab in subjects with BRVO

Overall Study Design

This is an ongoing, Phase 3, multicenter, randomized, double-masked, sham injection-controlled study of intravitreal ranibizumab compared with sham injections in subjects with macular edema secondary to BRVO. Approximately 380 subjects with BRVO were to be randomized at approximately 100 study sites.

The study consisted of a 28-day screening period (Days -28 to -1) and a 6-month treatment period (Day 0, and Months 1, 2, 3, 4, and 5), followed by a 6-month observation period (Month 6 through completion of the study at Month 12). Subjects had a final visit at Month 12. The study duration was 12 months, excluding the 28-day screening period. The primary analyses presented in this report are based on data from the 6 months treatment period. The 6-month observation period of the study is ongoing.

Subjects who provided consent entered the 28-day screening period to determine eligibility. As part of the screening process, the central reading center, the (b) (4) evaluated macular OCT images to determine subject eligibility. Subjects were required to meet the BCVA and retinal thickness eligibility requirements both during the screening period (as confirmed by the central reading center) and on Day 0 (as determined by the evaluating physician). After all of a subject's eligibility requirements were confirmed, site personnel telephoned the IVRS on Day 0 to randomize the subject.

Eligible subjects were randomized in a 1:1:1 so that approximately 130 subjects received monthly ranibizumab injections of 0.5 mg, approximately 130 subjects received monthly ranibizumab injections of 0.3 mg, and approximately 130 subjects received monthly sham injections during the treatment period. Randomization was stratified by the Day 0 BCVA score ($\leq$ 34 letters [approximately worse than 20/200] vs. 35-54 letters [approximately 20/200 to worse than 20/80] vs. $\geq$ 55 letters [approximately 20/80 or better] based on the ETDRS chart and assessment at a starting test distance of 4 meters, and by study center. A dynamic randomization method was used to obtain an approximately 1:1:1 ratio between the three treatment arms. The method was a generalization of the hierarchical method proposed by Signorini et al. (1993), designed to achieve overall balance, balance within each category defined by visual acuity score, and balance within each study center between the three treatment arms. A biased-coin assignment was used when the imbalance within a stratum exceeded a specified threshold.

Only one eye was chosen as the study eye. Only the study eye was treated with either ranibizumab injection or sham injection.

There must have been 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 (a qualified ophthalmologist), who was masked to treatment assignment and evaluated all ocular assessments including the need for rescue laser treatment. At least one other investigator (and designated assistants, as needed) was designated as the injecting physician, who was unmasked to treatment assignment and performed the study drug injections (ranibizumab or sham) but was masked to the dose of study drug (0.3 mg vs. 0.5 mg).

Either the injecting physician or the evaluating physician may have performed the laser rescue treatment if indicated. Once the roles of the evaluating and injecting physicians were designate, the roles could not be switched at any time during the 6-month treatment period. It should be noted that during a subject's observation period (Months 6 through 12), the evaluating physician could assume the role of the injecting physician. However, the converse was not true: The injecting physician could not assume the role of the evaluating physician during a subject's

observation period. Subjects, study site personnel (with the exception of site personnel performing or assisting with the injection procedure), the designated evaluating physician, central reading center personnel, and the Sponsor and its agents with the exception of drug accountability monitors) were masked to subject treatment assignment throughout the study.

Reviewer's Comment: *The use of sham control was discouraged by the agency.*

Treatment Period

Subjects had monthly visits during the 6-month treatment period for the evaluation of safety and efficacy. Subjects had either the first injection of intravitreal ranibizumab or a sham injection administered by the injecting physician on Day 0. Subjects returned for a safety assessment on Day 7 (± 2 days) after the first injection. At subsequent visits (every month), subjects had a safety evaluation performed by the evaluating physician prior to receiving an injection of ranibizumab or sham.

Subjects were contacted by site personnel 3 days (± 1 day) after each injection to elicit reports of 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, self-administered, post-injection antimicrobials.

In the sham injection arm, sham injections were administered according to the same dosing schedule as ranibizumab injections (i.e., every month during the 6-month treatment period).

Figure 6.1.3.1-1 Study Scheme

Month	0	1	2	3	4	5	6	7	8	9	10	11	12
	Treatment Period						Observation Period						
Sham arm (n = 130)	x	x	x	x/L	x	x	X	X	X	X/L	X	X	
0.3-mg ranibizumab arm (n = 130)	X	X	X	X/L	X	X	X	X	X	X/L	X	X	
0.5-mg ranibizumab arm (n = 130)	X	X	X	X/L	X	X	X	X	X	X/L	X	X	
							1° EP						

x=sham injection; X=0.3 mg or 0.5 mg intravitreal ranibizumab injection; L = laser (if indicated); X=ranibizumab injection (if indicated); 1°EP=primary endpoint.

L	L	Rescue treatment criteria (study eye) with laser at the Month 3 and 9 visits
Subject's best corrected visual acuity (BCVA) is 20/40 or worse (Snellen equivalent) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts or subject has mean central subfield thickness ≥250 µm on OCT **AND** Compared with the visit 3 months prior to the current visit, subject has BCVA gain <5 letters or a decrease <50 µm in mean central subfield thickness **Note:** If the subject did not meet above listed rescue criteria at the Month 3 visit, he or she was to be reassessed at the Month 4 visit and again at the Month 5 visit, if applicable. Similarly, if the subject did not meet the rescue treatment criteria at the Month 9 visit, he or she was to be reassessed at the Month 10 visit and again at the Month 11 visit, if applicable.		

X	Observation period (Months 6 through 11) retreatment criteria (study eye) for treatment with ranibizumab
Subject's BCVA is 20/40 or worse (Snellen equivalent) using ETDRS charts or subject has mean central subfield thickness ≥250 µm on OCT	

During the 6-month treatment period, dose holding of the intravitreal injection (ranibizumab or sham) applied for safety reasons related to either study drug or procedure (intravitreal injection).

In all three treatment arms, the evaluating physician determined the need for rescue laser treatment beginning at the Month 3 visit using criteria (Figure 6.1.3.1-1) that were based upon those established by the Branch Vein Occlusion Study (BVOS) (1984). If a subject did not meet the criteria for rescue treatment with laser at the Month 3 visit, he or she was reevaluated at subsequent monthly visits (Month 4 or Month 5) during the treatment period. Laser treatment was to be held for safety reasons related to the procedure.

Observation Period

After the 6-month treatment period, all subjects continued to be monitored for safety and efficacy outcomes at each monthly visit for the remainder of the 12-month period. During the 6-month observation period (beginning at the Month 6 visit), all subjects were evaluated monthly to determine the need for retreatment with ranibizumab.

Subjects randomized to the 0.3 mg ranibizumab dose group received the 0.3 mg dose if they qualified for retreatment, and subjects randomized to either the sham injection group or the 0.5 mg ranibizumab dose group received the 0.5 mg dose if they qualified for retreatment. Subjects received either a 0.3 mg or 0.5 mg ranibizumab injection if they met either of the following retreatment criteria in the study eye:

- BCVA of 20/40 or worse (Snellen equivalent) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, or
- Mean central subfield thickness of $\geq$ 250 μm on OCT

Subjects were evaluated each month during the observation period to determine the need for retreatment with ranibizumab.

Subjects were evaluated each month during the observation period to determine their eligibility for retreatment with ranibizumab. The last visit at which subjects could be eligible for retreatment with ranibizumab was Month 11. Subjects had a final visit at Month 12.

In all three treatment arms, the evaluating physician determined the need for rescue laser treatment at the Month 9 visit using criteria that were based upon those established by the BVOS (1984). If a subject did not meet the criteria for rescue treatment with laser at the Month 9 visit, he or she was re-evaluated at subsequent monthly visits (Month 10 or 11) during the observation period. Laser treatment was to be held for safety reasons related to the procedure.

All study subjects remained masked to their treatment assignment throughout the study. For subject who discontinued study treatment for any reason, every attempt was to be made to continue with the scheduled visit assessments.

Table 6.1.3.1-1 Clinical Sites - Study FVF4165g
* Also an Investigator in Study FVF4166g

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S15325 *	Prema Abraham, MD Rapid City, SD 13595	2	1	2	3	5 (1.3%)
S16398 *	D. Virgil Alfaro, MD Charleston, SC 13876	2	2	4	6	8 (2.0%)
S15698 *	Carl Awh, MD Nashville, TN 13953	1	2	1	3	4 (0.9%)
S15700 *	Carl Baker, MD Paducah, KY 19391	1	0	1	1	2 (0.5%)
S15357 *	Sophie Bakri, MD Colin McCannel, MD [1] Rochester, MN 20083	1	0	1	1	2 (0.5%)
S16397 *	Gaetano Barile, MD New York, NY 14120	0	1	0	1	1 (0.3%)
S18515 *	Michael Bennett, MD Honolulu, HI 18949	1	1	1	2	3 (0.8%)
S18785 *	Brian B. Berger, MD Austin, TX 13466	1	1	2	3	4 (0.9%)
S16409 *	Robert B. Bhisitkul, MD, PhD San Francisco, CA 12253	1	0	1	1	2 (0.5%)
S15385 *	Gregory Blaha, MD, PhD Peabody, MA 19294	1	1	1	2	3 (0.8%)
S16242 *	David Boyer, MD Beverly Hills, CA 13251	1	2	3	5	6 (1.5%)
S15331 *	H. Logan Brooks, Jr. MD Tallahassee, FL 14149	1	3	2	5	6 (1.5%)
S16485 *	David M. Brown, MD Houston, TX 13995	4	2	3	5	9 (2.3%)
S19677	Andrew Burrows, MD Englewood, NJ 19961	1	0	0	0	1 (0.3%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S16243 *	Charles Campbell, MD Corpus Christi, TX 19402	1	1	0	1	2 (0.5%)
S15387 *	Peter Campochiaro, MD Baltimore, MD 17521	3	5	3	8	11 (2.8%)
S15388 *	Ken Carnevale, MD Lynbrook, NY 19296	1	1	0	1	2 (0.5%)
S16507	Michael Cassell, MD Kansas City, MO 19470	0	1	0	1	1 (0.3%)
S15702	Clement Chan, MD Palm Springs, CA 19393	1	1	0	1	2 (0.5%)
S15676	Rangram Chandran, MD Modesto, CA 19337	3	1	1	2	5 (1.3%)
* S16399 S18007	Tom Chang, MD Pasadena, CA Hacienda Heights, CA 13253	1	1	0	1	2 (0.5%)
S19296 *	Nauman Chaudhry, MD New London, CT 16230	1	1	1	2	3 (0.8%)
S15334 *	Thomas A. Ciulla, MD Indianapolis, IN 10013	1	1	0	1	2 (0.5%)
S20389 *	W. Lloyd Clark, MD West Columbia, SC 14132	1	1	0	1	2 (0.5%)
S15389 *	Timothy Cleland, MD San Antonio, TX 19297	1	1	2	3	4 (1.0%)
S15703 *	Gary Cowan, MD Fort Worth, TX 19399	1	1	1	2	3 (0.8%)
S16247 *	Amr Dessouki, MD Campbell, CA 16090	1	0	1	1	2 (0.5%)
S15337 *	Richard Dreyer, MD Portland, OR 10015	0	0	1	1	1 (0.3%)
S16270 *	Pravin Dugel, MD Phoenix, AZ 17798	5	4	5	9	14 (3.5%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S16271	Alexander M. Eaton, MD Fort Myers, FL 13945	1	1	0	1	2 (0.5%)
S15651 *	Nicholas Engelbrecht, MD St. Louis, MO 20461	0	1	0	1	1 (0.3%)
S16384 *	David W. Faber, MD Salt Lake City, UT 19298	1	0	1	1	2 (0.5%)
S15391 *	Leonard Feiner, MD Teaneck, NJ 19299	5	8	6	14	19 (4.8%)
S18903 *	Robert Feldman, MD Altamonte Springs, FL 05498	0	0	1	1	1 (0.3%)
S16974	Philip Ferrone, MD Great Neck, NY 13395	2	1	2	3	5 (1.3%)
S19700 *	Gregory Fox, MD Shawnee Mission, KS 20012	1	2	1	3	4 (1.0%)
S19929 *	Ronald Frenkel, MD Stuart, FL 20722	1	0	0	0	1 (0.3%)
S20359 *	Ron Gallemore, MD Torrance, CA 21068	0	1	0	1	1 (0.3%)
S15333 *	Alan Gordon, MD Phoenix, AZ 16727	5	2	1	3	8 (2.0%)
S16464 *	Ernest Guillet, MD Rochester, NY 19471	1	1	4	5	6 (1.5%)
S17331	Sunil Gupta, MD Pensacola, FL 19948	2	2	1	3	5 (1.3%)
S15370 *	Seenu Hariprasad, MD Chicago, IL 13257	1	0	1	1	2 (0.5%)
S15706 *	Yu-Guang He, MD Dallas, TX 19343	1	1	1	2	3 (0.8%)
S16562 *	Jeffrey S. Heier, MD Boston, MA 10018	3	3	3	6	9 (2.3%)
S16253	Allen Ho, MD Philadelphia, PA 17787	2	1	1	2	4 (1.0%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S16254 *	Deborah Hoffert, MD Bangor, ME 19407	1	1	1	2	3 (0.8%)
S15645 S17782 *	John Hoskins, MD Knoxville, TN 19301	2	2	4	6	8 (2.0%)
S15341 *	Baker Hubbard, MD Atlanta, GA 14235	2	2	1	3	5 (1.3%)
S16563	Darmakusma Ie, MD Lawrenceville, NJ 13789	1	1	1	2	3 (0.8%)
S15343 *	Cameron Javid, MD [2] Leonard Joffe, MD Tucson, AZ 22054	1	2	2	4	5 (1.3%)
S16541 *	Robert Johnson, MD San Francisco, CA 10019	1	4	1	5	6 (1.5%)
S16386 *	Randy Katz, MD Boynton Beach, FL 14008	0	1	1	2	2 (0.5%)
S15710 *	Alan Kimura, MD Denver, CO 19344	0	1	0	1	1 (0.3%)
S15711 *	S. Young Lee, MD Abilene, TX 19345	8	8	7	15	23 (5.8%)
S15646 *	Nicholas Leonardy, MD Toledo, OH 19303	1	0	1	1	2 (0.5%)
S15372 *	Eugene Lit, MD Oakland, CA 19055	1	1	3	4	5 (1.3%)
S18791 *	Louis Lobes, MD Pittsburgh, PA 09771	1	1	1	2	3 (0.8%)
S15712 *	Everett Madson, MD Omaha, NE 19346	1	0	1	1	2 (0.5%)
S15355 *	Naresh Mandava, MD Aurora, CO 17911	1	0	1	1	2 (0.5%)
S15356 *	Dennis Marcus, MD Augusta, GA 13897	4	3	2	5	9 (2.3%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S16388 *	Mark Michels, MD, PA Palm Beach, FL 13872	2	1	1	2	4 (1.0%)
S16497 *	Robert Mittra, MD Edina, MN 16103	1	1	1	2	3 (0.8%)
S16465 *	George Novalis, MD Tucson, AZ 19483	1	1	0	1	2 (0.5%)
S16389 *	Arun Patel, MD Sacramento, CA 19429	2	3	5	8	10 (2.5%)
S16498 *	Matthew D. Paul, MD Danbury, CT 13506	1	1	0	1	2 (0.5%)
S19468	Peter R. Pavan, MD Tampa, FL 10023	0	1	0	1	1 (0.3%)
S16499	Dante Pieramici, MD Santa Barbara, CA 14254	2	1	1	2	4 (1.0%)
S16500 *	Jay G. Prensky, MD Camphill, PA 13505	1	3	1	4	5 (1.3%)
S19257	Robert Rosa, MD Temple, TX 13250	1	1	1	2	3 (0.8%)
S16390 *	Krista Rosenberg, MD Fort Lauderdale, FL 19677	2	2	2	4	6 (1.5%)
S15648 S18008 *	Daniel Roth, MD New Brunswick, NJ 19307	1	3	2	5	6 (1.5%)
S18790	Paul E. Runge, MD Sarasota, FL 13948	1	0	0	0	1 (0.3%)
S16269 *	David Saperstein, MD Seattle, WA 17922	0	1	0	1	1 (0.3%)
S16460 *	Todd Schneiderman, MD Silverdale, WA 14198	1	0	0	0	1 (0.3%)
S19347	Lisa Schocket, MD Baltimore, MD 20801	1	1	1	2	3 (0.8%)
S16392 *	Jerry Sebag, MD Huntington Beach, CA 13465	2	1	1	2	4 (1.0%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S16502 *	Michael Singer, MD San Antonio, TX 13525	2	3	2	5	7 (1.8%)
S16504 *	Brian Sippy, MD Missoula, MT 19316	1	3	3	6	7 (1.8%)
S16393 *	Allen Thach, MD Las Vegas, NV 11295	1	2	1	3	4 (1.0%)
S16561 *	Michael Tolentino, MD Winter Haven, FL 19318	3	4	4	8	11 (2.8%)
S18819 *	David Tom, MD Hamden, CT 13998	1	2	1	3	4 (1.0%)
S16505 *	Robert Torti, MD Desoto, TX 17684	1	1	1	2	3 (0.8%)
S16991 *	Erik Tu, MD Baldwin Park, CA 20022	0	0	1	1	1 (0.3%)
S15653 *	Allen Verne, MD Walnut Creek, CA 19292	0	1	1	2	2 (0.5%)
S16394 *	Thierry Verstraeten, MD Pittsburgh, PA 13844	2	1	1	2	4 (1.0%)
S15363 *	Joseph Walker, MD Fort Myers, FL 13787	2	1	2	3	5 (1.3%)
S15723 *	Paul Weishaar, MD Wichita, KS 19319	2	1	1	2	4 (1.0%)
S15727 *	Mark Wieland, MD Mountain View, CA 19320	1	1	1	2	3 (0.8%)
S16400 *	Matthew Wood, MD Lincoln, NE 19413	2	2	1	3	5 (1.3%)
S16506 *	William Wood, MD Lexington, KY 19322	2	3	5	8	10 (2.5%)
S16395 *	John Wroblewski, MD Hagerstown, MD 19754	2	1	1	2	4 (1.0%)
S19309 *	Lucy Young, MD Boston, MA 20794	0	0	1	1	1 (0.3%)

1 Dr. Bakri replaced Dr. McCannel as the Principal Investigator at this site.
2 Dr. Javid replaced Dr. Joffe as the Principal Investigator at this site.

Reviewer's Comments:
It is preferred that at least ten patients be randomized per treatment arm per clinical site to allow for an investigator interaction analysis.

Study Population

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

General Inclusion Criteria

1. Willingness to provide signed Informed Consent Form (including HIPAA authorization)
2. Age ≥ 18 years
3. For sexually active women of childbearing potential, use of an appropriate form of contraception (or abstinence) for the duration of the study
4. Ability and willingness to return for all scheduled visits and assessments

Ocular Inclusion Criteria (Study Eye)

5. Foveal center-involved macular edema secondary to BRVO

Subjects were screened at the time of diagnosis of BRVO but no longer than 12 months after diagnosis. The following definitions were used for the purposes of this study:

BRVO	An eye that had retinal hemorrhage or other biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in one quadrant or less of the retina drained by the affected vein. The presence of a BRVO was assessed on fluorescein angiography.
Hemiretinal vein occlusion (HRVO)	An eye that had retinal hemorrhage or other biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in more than one quadrant and up to three quadrants. Typically, an HRVO is an RVO that involves two altitudinal quadrants. For the purposes of this study, eyes with HRVO were treated the same as eyes with BRVO. The presence of HRVO was assessed on fluorescein angiography.

6. BCVA using ETDRS charts of 20/40 to 20/400 (Snellen equivalent) in the study eye
7. Mean central subfield thickness ≥ 250 µm on OCT measurements (at screening [confirmed by the central reading center, (b) (4) and Day 0 [confirmed by the evaluating physician])
8. Media clarity, pupillary dilation, and participant cooperation sufficient to obtain adequate fundus photographs

Exclusion Criteria

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

General Exclusion Criteria

1. History of cerebral vascular accident or myocardial infarction within 3 months prior to Day 0
2. History of any anti-VEGF treatment in fellow eye within 3 months prior to Day 0
3. History of any systemic anti-VEGF or pro-VEGF treatment within 6 months prior to Day 0
4. History of allergy to fluorescein
5. History of allergy to ranibizumab injection or related molecule
6. Relevant systemic disease that may be associated with increased systemic VEGF levels (namely, all active malignancies) History of successfully treated malignancies was not an exclusion criteria
7. Uncontrolled blood pressure (defined as a systolic value of > 180 mmHg and a diastolic value of > 110 mm Hg)
8. Pregnancy or lactation
9. Any condition that, in the opinion of the investigator, would preclude participation in the study (e.g., chronic alcoholism or drug abuse, personality disorder or use of major tranquilizers, indicated difficulty in long-term follow-up, and likelihood of survival of less than 1 year)
10. Participation in an investigational trial within 30 days prior to Day 0 that involved treatment with any drug (excluding vitamins and minerals) or device that had received regulatory approval at the time of study entry

Ocular Exclusion Criteria (Study Eye)

11. Prior episode of RVO
12. Brisk afferent pupillary defect
13. History of radial optic neurotomy or sheathotomy
14. History or presence of AMD (dry or wet form)
15. History of any anti-VEGF treatment in the study eye within 3 months prior to Day 0
16. History of laser photocoagulation for macular edema within 4 months prior to Day 0
    Note: If prior grid laser photocoagulation had been performed, the following two criteria had to be met:
    The current area of leakage must have extended into the fovea (i.e., prior laser treatment was inadequate).
    There was no evidence of laser damage to the fovea.
17. History of panretinal scatter photocoagulation or sector laser photocoagulation within 3 months prior to randomization or anticipated within the next 4 months following randomization
18. History of intraocular corticosteroid use within 3 months prior to Day 0
19. History of pars plana vitrectomy
20. History of intraocular surgery (including cataract extraction, scleral buckle, etc.) within 2 months prior to Day 0 or anticipated within the next 7 months following Day 0

21. History of yttrium-aluminum-garnet capsulotomy performed within 2 months prior to Day 0
22. Previous filtration surgery in the study eye
23. History of herpetic ocular infection
24. History of ocular toxoplasmosis
25. History of rhegmatogenous retinal detachment
26. History of idiopathic central serous chorioretinopathy
27. Evidence upon examination of vitreoretinal interface disease (e.g., vitreomacular traction, epiretinal membrane), either on clinical examination or OCT, thought to be contributing to macular edema
28. An eye that, in the investigator's opinion, would not benefit from resolution of macular edema, such as eyes with foveal atrophy, dense pigmentary changes, or dense subfoveal hard exudates
29. Presence of an ocular condition that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the study (e.g., uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass syndrome, or prior macula-off rhegmatogenous retinal detachment)
30. Visually significant hemorrhage obscuring the fovea and felt to be a major contributor to reduced visual acuity

    The subject was to be followed and when the hemorrhage in the fovea cleared to the point that it was no longer a major contributor to reduced visual acuity, the subject could be screened for the study.
31. Presence of a substantial cataract that, in the opinion of the investigator, was likely to have been decreasing visual acuity by 3 lines or more (i.e., a 20/40 cataract)
32. IOP $\geq$ 30 mmHg

    If a subject's IOP was $\geq$ 30 mmHg, that subject was to be referred for glaucoma treatment and could be re-screened after 1 month
33. Evidence upon examination of pseudoexfoliation
34. Aphakia
35. Evidence upon examination of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis
36. Evidence upon examination of any diabetic retinopathy, defined as eyes of diabetic patients with more than one microaneurysm outside the area of the vein occlusion (inclusive of both eyes)
37. Relevant ocular disease that may have been associated with increased intraocular VEGF levels (namely, uveitis, neovascular glaucoma, neovascular AMD, diabetic retinopathy, diabetic maculopathy, or ocular ischemic syndrome)
38. Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded by the central reading center
39. Improvement of > 10 letters on BCVA between screening and Day 0

Reviewer's Comment:
Acceptable.

Study Treatments

Ranibizumab Injection Treatment Arms

During the 6-month treatment period, subjects randomized to the ranibizumab treatment arms received intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) in a single-dose regimen given every month (Day 0 through the Month 5 visit), for a total of six injections. Subjects may have been eligible for retreatment with ranibizumab during the observation period (Month 6 through Month 11 visits) if they met the retreatment criteria.

Subjects randomized to ranibizumab arms may have received a maximum of 12 monthly injections of ranibizumab throughout the study. Missed injection doses were not replaced.

Sham Injection Treatment Arm

During the 6-month treatment period, subjects randomized to the sham injection received sham injections in a single-dose regimen given every month (Day 0 through the Month 5 visit), for a total of six sham injections. Subjects may have been eligible for retreatment with 0.5 mg ranibizumab injections during the observation period (Month 6 through Month 11 visits) if they met the retreatment criteria.

Subjects randomized to the sham arm may have received a maximum of six sham injection and six ranibizumab injections throughout the study. Missed injection doses were not replaced.

Rescue Treatment with Laser

In all three treatment arms, the evaluating physician determined the need for rescue laser treatment at the Month 3 visit using rescue criteria. If a subject did not meet the criteria for rescue treatment with laser at the Month 3 visit, he or she was to be re-evaluated at subsequent monthly visits (Month 4 or 5) during the treatment period.

Similarly, subjects in all three treatment arms may have qualified for the rescue treatment with laser at the Month 9 visit using the rescue criteria. As with the treatment period, if a subject did not meet the criteria for rescue treatment with laser at the Month 9 visit, he or she was to be re-evaluated at subsequent monthly visits (Month 10 or 11) during the observation period.

Removal of Subjects from Therapy or Assessment

Subjects could be discontinued from study treatment or the study for any of the following reasons: if it was in the best interest of the subject or because of intercurrent illness, adverse events, or worsening condition. The investigator could request the withdrawal of a subject because of non-compliance, administrative reasons, or any other valid and ethical reasons.

If a subject discontinued from study treatment, all attempts were to be made to continue with the subject's study assessments.

Subjects may have withdrawn from the study at any time. Any subject who withdrew before completing the study was encouraged to return to the study center for an early termination visit. If a subject discontinued from the study, he or she was not to be allowed to re-enter the study.

Prior and Concomitant Therapies
Concomitant medications were any prescription drugs or over-the-counter preparations other than protocol-specified medications (e.g., dilating drops, fluorescein dyes, etc.) and pre- and post-injection medications (e.g., proparacaine, antimicrobials, etc.) used by a subject within 7 days preceding Day 0 until conclusion of his or her study participation (Month 12) or early termination visit.

Subjects continued to receive all medications and standard treatment administered for their other conditions at the discretion of their physician except in the following instances:

- Concurrent use of any anti-VEGF agents (systemic or ocular, including commercially available Lucentis or Avastin) was not permitted. Any subject who received treatment with such an agent was discontinued from further study treatment.
- Concurrent use of intraocular corticosteroids was not allowed in the study eye.
- Concurrent daily use of oral corticosteroids to treat a chronic condition (e.g., arthritis, chronic lung disease, or other inflammatory condition) was not allowed.
- Concurrent treatment with injectable corticosteroids to treat a musculoskeletal condition (e.g., arthralgia, low back pain) was not allowed.
- Concurrent use of experimental therapies was not allowed.

Cataract surgery in the study eye may have been performed if clinically indicated and should have occurred 28 or more days after the last ranibizumab or sham injection; the next ranibizumab or sham injection was held for 28 or more days following cataract surgery.

Laser treatment in the fellow eye was permitted as per standard of care no sooner than 1 day preceding or following treatment in the study eye.

STATISTICAL METHODS

Outcome Measures
In the following sections, BCVA refers to BCVA in the study eye based on the ETDRS visual acuity chart and assessed at a starting test distance of 4 meters. In addition, all other ocular efficacy outcome measures refer to the study eye only.

Primary Efficacy Outcome Measures
The primary efficacy outcome measure was the mean change from baseline in the BCVA score at a starting test distance of 4 meters at 6 months.

Secondary Efficacy Outcome Measures
The secondary efficacy outcome measures for the treatment period of the study were the following:

- Proportion of subjects who gained ≥ 15 letters in BCVA score at 6 months compared to baseline

- Proportion of subjects who lost < 15 letters in BCVA score at 6 months compared with baseline
- Mean change from baseline in BCVA score over time up to 6 months
- Proportion of subjects with a central foveal thickness of ≤ 250 μm, assessed on OCT, at 6 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months

The following are the secondary efficacy outcome measures for the observation period of the study:

- Mean change from baseline in BCVA score over time up to 12 months
- Proportion of subjects who gain at least 15 letters in BCVA score at 12 months compared with baseline
- Proportion of subjects who lose fewer than 15 letters in BCVA score at 12 months compared with baseline
- Proportion of subjects with a central foveal thickness of ≤ 250 μm, assessed on OCT, at 12 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 12 months
- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 12 months
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 12 months

Safety Outcome Measures

- Incidence and severity of ocular adverse events
- Incidence and severity of non-ocular adverse events
- Changes and abnormalities in clinical laboratory parameters and ocular safety assessments (e.g., IOP and slit lamp)
- Incidence of positive serum antibodies to ranibizumab
- Changes in vital signs

Pharmacokinetic Outcome Measures

- Serum ranibizumab concentrations on Day 7 (± 2 days) (for the subset of subjects separately consenting to provide the optional additional pharmacokinetic samples)
- Serum ranibizumab concentrations (consisting of one required measurement for all subjects 7 days [+ 3 days} after the third dose)

- Serum ranibizumab concentrations 3 (± 2) days and 14 (± 2) days after the third dose and at the next scheduled visit prior to dosing (for the subset of subjects separately consenting to provide the optional additional pharmacokinetic samples)
- Ranibizumab concentrations consisting of required measurements for all subjects at the screening and Month 6 (pre-injection) visits

Assay Methods

Antibodies against ranibizumab were evaluated using a bridging homogenous ELISA method developed at Genentech. In this assay, the sample is [redacted]. In this assay, [redacted] indicated that the sample was confirmed positive for anti-ranibizumab antibodies. All confirmed positive samples were further characterized by titration.

A homogenous bridging ELISA was developed at Genentech to measure the concentration of ranibizumab in serum. In this assay, the sample is [redacted]

Analysis Populations

Intent-to-Treat Population

This population included all subjects randomized in the study. Treatment groups for this population were defined according to the treatment assigned at randomization. This population was used for summaries of demographics and study conduct and was the primary patient-analysis population used in the efficacy analyses.

Per-Protocol Subjects

This population included randomized subjects who were considered to be sufficiently compliant with the protocol, as defined in the Statistical Analysis Plan (SAP). Treatment groups for this population were defined according to the treatment assigned at randomization. This population was used in supportive sensitivity analyses for the primary efficacy endpoint and for the treatment-period secondary efficacy endpoint of the proportion of subjects who gained ≥ 15 letters in visual acuity score at 6 months compared with baseline.

Safety-Evaluable Subjects
This population included randomized subjects who received at least one injection of study drug (ranibizumab or sham) during the 6-month treatment period (Day 0 to Month 5 treatments). Treatment groups for this population were defined according to the actual treatment received as follows:

- Sham: subjects who received only sham injections (i.e., no active treatment) during the 6-month treatment period
- 0.3 mg ranibizumab: subjects who received at least one 0.3 mg ranibizumab injection but no 0.5 mg ranibizumab injections during the 6-month treatment period
- 0.5 mg ranibizumab: subjects who received at least one 0.5 mg ranibizumab injection during the 6-month treatment period

Pharmacokinetic-Evaluable Subjects
This population included all randomized subjects who received at least one injection of study drug (ranibizumab or sham) and who provided at least one sample for the determination of the serum concentration of ranibizumab. Treatment groups for this population were defined according to the treatment assigned at randomization.

Efficacy Analyses
Efficacy endpoints were analyzed on the basis of the ITT population, with subjects grouped according to the treatment assigned at randomization. Missing values were imputed using the last-observation-carried-forward (LOCF) method.

For the treatment-period endpoints, comparisons of efficacy endpoints were performed between each of the ranibizumab dose groups and the sham-injection (control) group. All pairwise comparisons for a 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 sham group (see below). For the treatment-period secondary efficacy endpoints, adjustments for multiplicity of endpoints were also made to manage the type 1 error rate.

Unless otherwise noted, efficacy analyses were stratified by baseline (Day 0) BCVA score in the study eye (≤ 34, 35-54, ≥ 55 letters). Analysis of variance (ANOVA) or analysis of covariance (ANCOVA) models were used to analyze continuous endpoints. Cochran-Mantel-Haenszel (CMH) χ^2 tests were used to compare the proportion of subjects between treatment groups for most binary endpoints. For binary endpoints for which the proportion of subjects with the event was anticipated to be low or high, Fisher's exact test was used. All statistical tests were two-sided.

In addition to p-values for statistical tests, the estimates and confidence intervals (CIs) were provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between two treatment groups. All CIs were two-sided and at the 95% level.

Primary Efficacy Analysis
The mean change from baseline in BCVA score at 6 months was compared between each ranibizumab group and the sham-injection (control) group using an ANOVA model stratified by baseline BCVA score in the study eye (≤ 34, 35-54, ≥ 55 letters), with no additional covariate adjustment. Supportive sensitivity analyses for the primary endpoint were performed and are described in the SAP.

The Hochberg-Bonferroni multiple comparison procedure was used to adjust for comparisons of the two ranibizumab groups with the sham injection group to maintain an overall type 1 error rate of 0.05. If the p-values for both comparisons were ≤ 0.05, both ranibizumab groups were considered to be statistically significantly different from the sham group. If the p-value for the comparison of one ranibizumab group with the sham group was > 0.05, the other ranibizumab group was considered to be statistically significantly different from the sham group only if the p-value for its comparison with the sham group was ≤ 0.05/2 (0.025).

Secondary Efficacy Analyses
The following efficacy outcome measures from the 6-month treatment period were compared between each ranibizumab group and the sham-injection group using the CMH χ^2 test stratified by baseline BCVA score in the study eye (≤ 34, 35-54, ≥ 55 letters):

- Proportion of subjects who gained ≥ 15 letters in BCVA score at Month 6 compared with baseline
- Proportion of subjects with a central foveal thickness ≤ 250 μm at Month 6

The following efficacy outcome measure from the 6-month treatment period was compared between each ranibizumab group and the sham-injection group using Fisher's exact test:

- Proportion of subjects who lost < 15 letters in BCVA score at Month 6 compared with baseline

The following efficacy outcome measures from the 6-month treatment period were compared between each ranibizumab group and the sham-injection group using an ANOVA or ANCOVA model:

- Mean change from baseline in BCVA score over time up to 6 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months

Type I Error Management Plan for Secondary Outcome Measures
To manage the type 1 error rate while testing multiple secondary efficacy endpoints for statistical significance, a type 1 error management plan was implemented.

Provided that a given ranibizumab dose group was statistically different from the control group in the primary endpoint, the secondary efficacy endpoints based on the 6-month treatment period were tested comparing that ranibizumab dose group with the control group. To manage the type I error rate, the secondary efficacy endpoints for the 6-month treatment period were prioritized and a hierarchical testing approach was used. Secondary efficacy endpoints that were closely related and of similar priority were grouped and tested as one stage in the hierarchy, with a Hochberg-Bonferroni multiple comparison procedure used at that stage. OCT endpoints were considered separately because they support the mechanism of action behind the primary endpoint.

The applicant's procedure is intended to manage the type I error rate among the secondary efficacy endpoints of visual acuity and visual function at 6 months within the dose group (not across dose groups) and, separately, among the OCT endpoints at 6 months.

Visual Acuity and Visual Function Endpoints
Contingent upon statistical significance in the primary endpoint for a given ranibizumab dose group, the secondary endpoints related to visual acuity and visual function were compared between that ranibizumab dose group and the control group using a hierarchical testing procedure with two stages, with higher priority endpoints in the earlier stage. An alpha level of 0.05 was used at each stage. Stages 1 and 2 each included two closely related endpoints with equal priority. For each stage, a Hochberg-Bonferroni procedure was used to control the type I error within the stage. If none of the endpoints at the first stage were statistically different between the given ranibizumab dose group and the control group, then the tests for the second stage will be considered not statistically significant regardless of the p-values from those tests.

Stage 1. The following endpoints will be tested using the Hochberg-Bonferroni procedure at an overall α level of 0.05:

- Proportion of subjects who gain at least 15 letters in BCVA score at 6 months compared with baseline
- Proportion of subjects who lose fewer than 15 letters in BCVA score at 6 months compared with baseline

Testing will proceed to Stage 2 if the ranibizumab dose is declared significantly different from control for at least one of the two endpoints.

Stage 2. If testing proceeds to Stage 2, then the following endpoints will be tested using the Hochberg-Bonferroni testing procedure at an overall α level of 0.05:

- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months (defined as successful if the comparison at Month 6 is statistically significant)
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months (defined as successful if the comparison at Month 6 is statistically significant)

This hierarchical testing procedure, in combination with the Hochberg-Bonferroni adjustment for multiplicity, results in strong control of the type I error rate at 0.05 within each of Stages 1 and 2 (Hochberg 1988). This procedure controls the overall type I error rate among the four secondary endpoints at ≤ 0.05 under any set of null hypotheses such that for Stage 1 or 2, when the null hypothesis is assumed for one endpoint within the stage, the null hypothesis is also assumed for the other endpoint within the stage.

For mean change from baseline in BCVA score over time up to 6 months, the procedure used to determine the earliest timepoint with a statistically significant difference will be performed for a given ranibizumab dose group if the testing procedure for the primary endpoint declares the difference between that ranibizumab dose group and the control group at Month 6 statistically significant. For mean changes from baseline in the NEI VFQ-25 near activities subscale and the NEI VFQ-25 distance activities subscale, the procedure used to determine the earliest timepoint with a statistically significant difference will be performed for a given ranibizumab dose group if the above hierarchical testing procedure declares the difference between that ranibizumab dose group and the control group at Month 6 statistically significant. For all three endpoints, beginning at Month 5 and moving backward, the test for a treatment difference at each timepoint will be performed at a significant level of 0.05. The procedure will stop at a given timepoint if the p-value of that timepoint's test is greater than 0.05.

OCT Endpoints
The two secondary endpoints based on OCT at Month 6 will be considered separately from the other secondary endpoints because they support the mechanism of action behind the primary endpoint. Contingent upon statistical significance in the primary endpoint for a given ranibizumab dose group, the following endpoints will be tested using the Hochberg-Bonferroni procedure at an overall α level of 0.05:

- Proportion of subjects with a central foveal thickness of ≤ 250 µm, assessed on OCT, at 6 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months (defined as successful if the comparison at Month 6 is statistically significant)

For mean changes from baseline in central foveal thickness, the procedure used to determine the earliest timepoint with a statistically significant difference will be performed for a given ranibizumab dose group if the above testing procedure declares the difference between that ranibizumab dose group and the control group at Month 6 statistically significant. Beginning at Month 5 and moving backward, the test for a treatment difference at each timepoint will be performed at a significance level of 0.05. The procedure will stop at a given timepoint if the p-value of that timepoint's test is greater than 0.05.

Efficacy Outcome Measures for the 6-Month Observation Period
Analyses based on the 6-month observation period data will be performed when all subjects have completed the study or discontinued early from the study. As the 6-month observation period of

the study is ongoing at the time of this report, analyses of the observation period data are not presented.

Pharmacokinetic Analyses
Serum concentrations of ranibizumab were summarized descriptively by treatment group and timepoint on the basis of the pharmacokinetic-evaluable population.

Safety Analyses
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 endpoints were analyzed for the safety-evaluable population with subjects grouped according to the actual treatment received. Safety summaries for this clinical study report (CSR) include data from the 6-month treatment period.

Determination of Sample Size
The sample size was determined based on the primary efficacy endpoint. The sample size of 390 subjects (130 subjects per treatment group) provided 90% power in the ITT analysis to detect a statistically significant difference between one or both ranibizumab groups and the sham group in the mean change from baseline in BCVA score at 6 months, assuming a mean change from baseline in BCVA score at 6 months of +12, +10, and +2 letters for the 0.5 mg, 0.3 mg, and sham-treated subjects, respectively, and assuming a standard deviation for the change from baseline in BCVA score at 6 months of 20 letters for each of the ranibizumab groups and of 28 letters for the sham-injection group. Calculations were based on a 1:1:1 randomization ratio (0.5 mg ranibizumab, 0.3 mg ranibizumab, vs. sham injection), and the Hochberg-Bonferroni multiple comparison procedure with an overall alpha level of 0.05. The power of the Hochberg-Bonferroni multiple comparison procedure was evaluated using Monte Carlo simulations.

Reviewer's Comment:
Mean changes less than 15 letters are not necessarily considered clinically significant.

Missing Data
For efficacy analyses, missing values were imputed using the LOCF method. Sensitivity analyses based on observed cases only (i.e., no imputation) and worst-outcome imputation were performed for key efficacy endpoints.

Changes to Planned Analyses
The Statistical Analysis Plan which was finalized on 10 April 2008 was amended on 16 June 2009. The amendment noted that, based on current masked data, the proportion of subject with a BCVA Snellen equivalent of 20/200 or worse at 6 months appeared to be low. Similarly, the proportion of subjects who lost < 15 letters in BCVA score at Month 6 compared with baseline appeared to be high. Therefore, for these two endpoints, statistical analyses on the basis of exact methods are appropriate, and the amendment to the SAP changed the analysis method for these two endpoints from large sample methods to exact methods.

Table 6.1.3.1-2
Study Flowchart: Screening, Treatment Period, Observation Period, and Early Termination Assessments

	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
Informed Consent	x															
Inclusion/Exclusion Criteria	x	x														
Demographic data	x															
Medical and surgical history	x															
NEI VFQ-25 [b]		x		x		x			x							
OARS questionnaire [b]		x		x		x			x						x	x
Physical exam	x														x	x
Vital signs [c, d]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Height (screening only) and weight	x														x	x
Serum pregnancy test [c, e]	x															
Urine pregnancy test [e]						x			x			x			x	x
Laboratory samples (hematology, serum chemistry, coagulation, and urinalysis) [c]	x														x	x
Serum anti-ranibizumab antibody sample [c]	x								x						x	x
Serum ranibizumab concentration sample [c]	x				x [f]				x						x	x
Optional serum ranibizumab concentration sample (PK subset only) [c]			x [g]		x [h]											
Optional plasma sample [c]	x								x						x	x
Optional aqueous humor sample [c] (selected sites only)		x							x						x	x
Best corrected visual acuity (4 meter starting distance) [c, i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lens status assessment		x							x						x	x

	Screen	Treatment Phase							Month							Early Term.[a]
	Day															
	-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
Reading speed [c] (subjects who read English fluently)		x		x		x			x						x	x
Contrast sensitivity [c]		x		x		x			x						x	x
Slitlamp Examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus Photography [j]	x	x				x			x [k]			x			x	x
Fluorescein Angiography [j]	x	x [k]				x			x [k]			x			x	x
OCT	x [j]	x [j, k]	x	x	x	x [j]	x	x	x [j, k]	x	x	x [j]	x	x	x [j]	x [j]
Intraocular pressure [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laser administration							x [m]					x [m]				
Call IVRS [n]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration [o, p]		x		x	x	x	x	x	Per retreatment criteria, no more than every 30 days							
Finger count, hand motion, light perception (when indicated) [q]		x		x	x	x	x	x	x	x	x	x	x	x		
Menstrual cycle recording [e]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [r]	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 [s]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact		x		x	x	x	x	x	x	x	x	x	x	x		

a For subjects who withdrew or were discontinued early from the study, performed 30 days (± 7 days) following the last injection of study drug or the last study visit.

b The NEI VFQ-25 was to be administered to subects by designated site personnel first, followed by the OARS questionnaire; these questionnaires were to be administered only to subjects who were fluent in English or Spanish.

c Performed pre-injection and before dilating eyes at all visits.

d Vital signs included blood pressure, respiration, pulse,and temperature.

e Performed for women of childbearing potential.

f Collected serum sample for all subjects 7 days (+3 days) after the third dose.

g Serum sample was to be drawn for subjects in the optional PK subset on Day 7 (± 2 days).

h For the PK subset, serum samples were to be drawn from subjects 3 (± 2) days and 14 (± 2) days after the third dose and at the next visit prior to the next dose. In the event that a subject missed PK draws after the third dose, the subject could have had the serum sample drawn after the fourth, fifth, or sixth dose. Subjects had to complete the PK sampling within a given monthly dosing interval.
i Performed before dilating eyes except at the final or early termination visit.
j The central reading center, (b) (4) evaluated fundus photographs, OCT images, and fluorescein angiograms of the study eye at the screening, Month 3, 9, and 12 visits, or early termination visit, and of both eyes at the Day 0 and Month 6 visits. OCT scans from all other visits were forwarded to the (b) (4) for grading and/or storage.
k At the Day 0 and the Month 6 visits, a fundus photograph, fluorescein angiogram, and OCT scan were also obtained of the fellow eye.
l Obtained pre-injection for both eyes and 60 minutes (± 10 minutes) post-injection for the study eye only. Obtained any time for both eyes at the safety assessment, final, or early termination visit. The method for determination of intraocular pressure used for a subject was to remain consistent throughout the study.
m Laser treatment could have been applied at the Months 3 and 9 visits (see note below) if a subject fulfilled the following rescue treatment criteria for the study eye: BCVA was 20/40 or worse (Snellen equivalent) using ETDRS charts, or mean central subfield thickness ≥ 250 µm on OCT, AND compared with the value at Month 3 visit prior to the current visit, the subject was reassessed a the Month 4 visit and again at the Month 5 visit, if applicable. Similarly, if a subject did not meet rescue treatment criteria at the Month 9 visit, the subject was reassessed at the Month 10 visit and again at the Month 11 visit, if applicable. Laser treatment was held for safety reasons.
n The IVRS was called to assign the study treatment or to terminate the subject from the study if it was the final visit (Month 12) or early termination visit.
o Study drug (ranibizumab or sham) administration was mandatory during the treatment period. During the observation period, subjects whose BCVA in the study eye using ETDRS charts was 20/40 or worse (Snellen equivalent) or who had a mean central subfield thickness in study eye ≥ 250 µm on OCT were eligible to receive retreatment with ranibizumab injection. Treatment was assigned by IVRS after site answers system's retreatment criteria questions.
p Site personnel ensured subjects had taken antimicrobials as prescribed prior to injection. Subjects were instructed again to take antimicrobials four times daily for 3 days post-injection and four times daily prior to their next injection.
q Performed within 15 minutes post-injection for the study eye only. Finger counting was tested for each subject after each injection; hand motion and light perception were tested when necessary.
r Recorded any concomitant medications used by the subject within 7 days preceding Day 0 (i.e., any prescription medication or over-the-counter preparations other than protocol-specified procedural medications and pre-injection and post-injection medications [e.g., proparacaine, anti-microbials, etc).
s Adverse events (AEs) were recorded on CRFs starting on Day 0 through the last study visit. AEs assessed by the physician as related to ranibizumab wee to be followed until the event resolved or was assessed as irreversible, chronic, or stable, even if the subject's participation in the study was over.
t Subjects were to be contacted 3 days (± 1 day) following treatment with study drug to elicit reports of any decreases in vision, eye pain, unusual redness, or any other new ocular symptoms. Subjects were also asked whether they had taken the prescribed, self-administered, post-injection antimicrobials.

Table 6.1.3.1-3 Analysis Populations

Analysis Population	Sham (N=132)	Ranibizumab	
		0.3 mg (N=134)	0.5 mg (N=131)
Randomized subjects (ITT)	132 (100%)	134 (100%)	131 (100%)
Per-protocol subjects	109 (82.6%)	111 (82.8%)	106 (80.9%)
Safety-evaluable subjects	131 (99.2%)	134 (100%)	130 (99.2%)
Pharmacokinetic-evaluable subjects	130 (98.5%0	133 (99.3%)	128 (97.7%)

Reviewer's Comment:
The analysis populations were similar in number across treatment groups.

Table 6.1.3.1-4 Subject Disposition and Reason for Discontinuation during the 6-Month Treatment Period (Randomized Subjects)

Status/Reason for Discontinuation	Number (%) of Subjects		
	Sham (n=132)	Ranibizumab	
		0.3 mg (n=134)	0.5 mg (n=131)
Received study drug	131 (99.2%)	134 (100%)	130 (99.2%)
Completed study through Month 6	123 (93.2%)	128 (95.5%)	125 (95.4%)
Discontinued treatment [a] at or prior to Month 5	9 (6.8%)	5 (3.7%)	5 (3.8%)
Death	0	0	0
Adverse event	0	0	2 (1.5%)
Lost to follow-up	0	1 (0.7%)	0
Physician's decision	1 (0.8%)	1 (0.7%)	3 (2.3%)
Subject's decision	7 (5.3%)	3 (2.2%)	0
Subject's condition mandated other therapeutic intervention	1 (0.8%)	0	0
Discontinued study prior to Month 6	9 (6.8%)	6 (4.5%)	6 (4.6%)
Death	0	0	1 (0.8%)
Adverse event	0	0	1 (0.8%)
Lost to follow-up	0	1 (0.7%)	0
Physician's decision	1 (0.8%)	1 (0.7%)	3 (2.3%)
Subject's decision	7 (5.3%)	4 (3.0%)	1 (0.8%)
Subject's condition mandated other therapeutic intervention	1 (0.8%)	0	0

a Subjects could remain in the study after treatment discontinuation.

Reviewer's Comment:
Three hundred and seventy six subjects completed Month 6 (94.7%). At or prior to Month 5, more subjects discontinued the study from the sham group (6.8%) than either the ranibizumab 0.3 mg group (3.7%) or the ranibizumab 0.5 mg group (3.8%).

The major reason for treatment/study discontinuation was 'Subject's Decision'.

Table 6.1.3.1-5 Major Protocol Deviations during the 6-Month Treatment Period Randomized Subjects

Deviation	Sham (N=132)	Ranibizumab	
		0.3 mg (N=134)	0.5 mg (N=131)
Any deviation	**23 (17.4%)**	**23 (17.2%)**	**25 (19.1%)**
Missing baseline or Month 6 visual acuity score for the study eye [a]	11 (8.3%)	8 (6.0%)	8 (6.1%)
Violation of study eligibility criterion that was not approved by the Sponsor	9 (6.8%)	10 (7.5%)	12 (9.2%)
Treatment error: wrong dose or study drug administered	0	0	1 (0.8%)
Anti-VEGF usage during the study	1 (0.8%)	0	0
Concurrent use of intraocular corticosteroids in study eye	0	0	1 (0.8%)
Concurrent daily use of oral corticosteroids to treat a chronic condition	1 (0.8%)	0	1 (0.8%)
Concurrent treatment with injectable corticosteroids to treat a musculoskeletal condition	2 (1.5%)	3 (2.2%)	3 (2.3%)
Treatment assignment unmasked	1 (0.8%)	4 (3.0%)	4 (3.1%)

Note: Table entries are number (%) of subjects with at least one deviation of the type specified.
a All subjects with this deviation had missing Month 6 visual acuity scores for the study eye.

Reviewer's Comments:
The number of major protocol deviations was comparable across the treatment groups.

The most frequent protocol deviations were missing baseline or Month 6 visual acuity score for the study eye or violation of study eligibility criteria.

Table 6.1.3.1-6 Discontinued Subjects and Reason
Study FVF4165g

Study Site ID	Subject ID	Reason for Discontinuation	Study Day	Visual Acuity (Letters)	
				Day 0	Last
Sham Group					
S15331	14801	Subject's Decision	116	64	67
S15333	10102	Subject's Decision	77	71	92
S15468	14701	Subject's Decision	128	36	20
S15711	10216	Subject's Decision	66	52	57
S15712	12502	Subject's Decision	57	54	34
S16390	11403	Physician's Decision to Withdraw		69	69
S16498	16701	AE - Subject's condition mandated other therapeutic intervention --cataract extraction and Avastin for worsening ME	33	50	52
S16562	14405	Subject's Decision	34	72	66
S19296	19203	Subject's Decision	72	25	23
0.3 mg Group					
S15325	10302	AE - Physician's Decision to Withdraw - Worsening Alzheimer's type dementia	53	72	75
S15372	10903	Lost to Follow-Up	92	52	50
S15653	13002	Subject's Decision	65	56	60
S16242	13106	Subject's Decision	186	25	31
S16485	11703	Subject's Decision	18	49	60
S16502	16301	Subject's Decision	30	47	51
0.5 mg Group					
S15391	11503	Physician's Decision to Withdraw	56	59	69
S16247	17401	Subject's Decision	176	42	86
S16270	14913	AE – Herpes Zoster oticus	163	69	61
S16393	16603	Physician's Decision to Withdraw		40	40
S16398	17908	Physician's Decision to Withdraw	88	48	44
S16502	16307	AE - Endophthalmitis	132	55	26
S16506	11009	Death – Cerebral hemorrhage	177	60	61

Table 6.1.3.1-7 Prior Therapies for Retinal Vein Occlusion in the Study Eye Randomized Subjects

Characteristics		Ranibizumab	
	Sham	0.3 mg	0.5 mg
Any prior therapy for RVO	25 (18.9%)	25 (18.7%)	21 (16.0%)
Anti-VEGF treatment	8 (6.1%)	10 (7.5%)	7 (5.3%)
Triamcinolone	10 (7.6%)	5 (3.7%)	10 (7.6%)
Other [a]	17 (12.9%)	14 (10.4%)	13 (9.9%)

a All therapies identified as "other" involved laser therapy.

Reviewer's Comment:
Approximately 16-19% of subjects had prior therapy for retinal vein occlusion in the study eye.

Table 6.1.3.1-8 Rescue Treatment with Laser in the Study Eye during the 6-Month Treatment Period Randomized Subjects

Characteristics	Sham n=132	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=131
Laser administered [a]	72 (54.5%)	25 (18.7%)	26 (19.8%)
Type of laser administered			
n	72	25	26
Focal	34 (47.2%)	12 (48.0%)	11 (42.3%)
Grid	41 (56.9%)	13 (52.0%)	16 (61.5%)
Panretinal photocoagulation	1 (1.4%)	0	0

a At any time during the 6-month treatment period.

Reviewer's Comment:
Approximately 55% of subjects in the sham treatment groups and 19-20% of the ranibizumab groups received laser rescue therapy in the study eye during the 6-month treatment period.

6.1.3.2 **Study FVF4166g:** A Phase 3, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion

Reviewer's Comment:
The Phase 3 clinical development plan for the retinal vein occlusion indication included two studies, FVF4165g and FVF4166g, submitted in this Supplement. The overall study designs of the trials are similar in terms of treatment schedule, study assessments, and primary and secondary efficacy endpoints. The studies differ in the subtype of retinal vein occlusion enrolled and otherwise have essentially the same inclusion and exclusion criteria. An additional major difference is that Study FVF4165g provided laser photocoagulation as rescue treatment in all treatment groups, beginning at Month 3. Study FVF4166g did not offer rescue treatment.

Primarily, the areas of difference between the two studies are presented here.

Primary Objectives:

1. To evaluate the efficacy of intravitreal injections of ranibizumab administered monthly for 6 months in the improvement of visual acuity as measured by the mean change in best corrected visual acuity (BCVA) at 6 months compared with baseline
- To evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly for 6 months, followed by a 6-month observation period with protocol-specified retreatment criteria

Secondary Objectives:

- To evaluate the efficacy of intravitreal injections of ranibizumab administered monthly for 6 months with respect to visual acuity outcomes (other than mean change in BCVA score at 6 months compared with baseline), anatomic outcomes, and patient-reported visual function outcomes
- To evaluate the pharmacokinetics of ranibizumab in subjects with central retinal vein occlusion (CRVO)

Overall Study Design
The overall study design of Study FVF4166g was the same as Study FVF4165g in terms of treatment schedule, study assessments, and primary and secondary efficacy endpoints. Study FVF4166g differed in that laser photocoagulation as a rescue treatment was offered to all treatment groups after Month 3.

The study scheme is presented in Figure 6.1.3.2-1 below.

Figure 6.1.3.2-1 Study Scheme

Month	0	1	2	3	4	5	6	7	8	9	10	11	12
	Treatment Period						Observation Period						
Sham arm (n=130)	x	x	x	x	x	x	X	X	X	X	X	X	
0.3-mg ranibizumab arm (n=130)	X	X	X	X	X	X	X	X	X	X	X	X	
0.5-mg ranibizumab arm (n=130)	X	X	X	X	X	X	X	X	X	X	X	X	
							1° EP						

x=sham injection; X=0.3-mg or 0.5-mg intravitreal ranibizumab injection; X=ranibizumab injection (if indicated); 1°EP=primary endpoint.

X	Observation period (Months 6–11) retreatment criteria (study eye) for treatment with ranibizumab
	Subject's best corrected visual acuity (BCVA) is 20/40 or worse (Snellen equivalent) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts or subject has mean central subfield thickness ≥ 250 µm on OCT.

Reviewer's Comment:
No rescue treatment was offered in this study.

Study Population
Subjects with macular edema secondary to CRVO were enrolled in the study. Written informed consent was obtained, and subjects were screened for eligibility before initiation of any study procedures.

Inclusion Criteria
Subjects had to meet the following inclusion criteria to be eligible for study entry:
Ocular Inclusion Criteria (Study Eye)

1. Foveal center-involved macular edema secondary to CRVO
Subjects were screened at the time of diagnosis of CRVO but no longer than 12 months after diagnosis. The following definitions were used for the purposes of this study:

CRVO	An eye that had retinal hemorrhage or other biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in three quadrants or more of the retina drained by the affected vein. The presence of a CRVO was assessed on fluorescein angiography

2. BCVA using ETDRS charts of 20/40 to 20/320 (Snellen equivalent) in the study eye

3. Mean central subfield thickness ≥ 250 µm on OCT measurements (at screening [confirmed by the central reading center, (b)(4) and Day 0 [confirmed by the evaluating physician])
4. Media clarity, pupillary dilation, and participant cooperation sufficient to obtain adequate fundus photographs

Reviewer's Comment:
The General Inclusion Criteria and Exclusion Criteria for Study FVF4166g were identical to those in Study FVF4165g. The Ocular Inclusion Criteria differed from Study FVF4165g and are presented below.

Study Treatments
Ranibizumab Injection Treatment Arms
During the 6-month treatment period, subjects randomized to the ranibizumab treatment arms received intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) in a single-dose regimen given every month (Day 0 through the Month 5 visit), for a total of six injections. Subjects may have been eligible for retreatment with ranibizumab during the observation period (Month 6 through Month 11 visits) if they met the retreatment criteria.

Subjects randomized to ranibizumab arms may have received a maximum of 12 monthly injections of ranibizumab throughout the study. Missed injection doses were not replaced.

Sham Injection Treatment Arm
During the 6-month treatment period, subjects randomized to the sham injection received sham injections in a single-dose regimen given every month (Day 0 through the Month 5 visit), for a total of six sham injections. Subjects may have been eligible for retreatment with 0.5 mg ranibizumab injections during the observation period (Month 6 through Month 11 visits) if they met the retreatment criteria.

Subjects randomized to the sham arm may have received a maximum of six sham injection and six ranibizumab injections throughout the study. Missed injection doses were not replaced.

STATISTICAL METHODS
The Outcome Measures for primary efficacy, secondary efficacy, safety, and pharmacokinetics were the same in Study FVF4165g and FVF4166g.

Reviewer's Comment:
The analysis populations were defined the same way in Study FVF4166g and FVF4165g.

Table 6.1.3.2-1 Study Investigators
* Also an Investigator in Study FVF4165g

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab 0.3 mg N=140	Ranibizumab 0.5 mg N=140	Ranibizumab Pooled N=280	All Subjects N=423
S15832 *	Prema Abraham, MD Rapid City, SD 13595	2	1	1	2	4 (1.0%)
S16405 *	D. Virgil Alfaro, III, MD Charleston, SC 13876	3	2	2	4	7 (1.8%)
S15569 *	Carl Awh, MD Nashville, TN 13953	1	1	1	2	3 (0.8%)
S15833	Wilson Baber, MD Shreveport, LA 19398	0	1	0	1	1 (0.3%)
S15680 *	Carl Baker, MD Paducah, KY 19391	3	2	6	8	11 (2.8%)
S15483 *	Sophie Bakri, MD Colin McCannel, MD [1] Rochester, MN 20083	0	1	0	1	1 (0.3%)
S16527 *	Gaetano Barile, MD New York, NY 14120	1	1	1	2	3 (0.8%)
S18516 *	Michael Bennett, MD Honolulu, HI 18949	1	2	1	3	4 (1.0%)
S18799 *	Brian B. Berger, MD Austin, TX 13466	1	1	1	2	3 (0.8%)
S16528 *	Robert B. Bhisitkul, MD, PhD San Francisco, CA 12253	1	0	0	0	1 (0.3%)
S15385 *	Gregory Blaha, MD, PhD Peabody, MA 19294	1	1	1	2	3 (0.8%)
S16529 *	David Boyer, MD Beverly Hills, CA 13251	5	4	3	7	12 (3.1%)
S15858 *	H. Logan Brooks, Jr. MD Tallahassee, FL 14149	0	1	0	1	1 (0.3%)
S16531 *	David M. Brown, MD Houston, TX 13995	3	3	5	8	11 (2.8%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S15732 *	Charles Campbell, MD Corpus Christi, TX 19402	1	0	1	1	2 (0.5%)
S15861 *	Peter Campochiaro, MD Baltimore, MD 17521	4	7	3	10	14 (3.6%)
S15455 *	Ken Carnevale, MD Lynbrook, NY 19296	1	1	2	3	4 (1.0%)
S17973 *	Tom Chang, MD Hacienda Heights, CA 13253	0	1	1	2	2 (0.5%)
S19297 *	Nauman Chaudhry, MD New London, CT 16230	0	1	0	1	1 (0.3%)
S15866 *	Thomas A. Ciulla, MD Indianapolis, IN 10013	1	0	0	0	1 (0.3%)
S20390 *	W. Lloyd Clark, MD West Columbia, SC 14132	1	1	1	2	3 (0.8%)
S15458 *	Timothy Cleland, MD San Antonio, TX 19297	1	0	0	0	1 (0.3%)
S15867 *	Gary Cowan, MD Fort Worth, TX 19399	0	0	1	1	1 (0.3%)
S17740	Uday Desai, MD Detroit, MI 21536	0	1	0	1	1 (0.3%)
S16534 *	Amr Dessouki, MD Campbell, CA 16090	3	3	4	7	10 (2.6%)
S15459 *	Richard Dreyer, MD Portland, OR 10015	0	0	1	1	1 (0.3%)
S16535 *	Pravin Dugel, MD Phoenix, AZ 17798	2	3	3	6	8 (2.0%)
S15496 *	Nicholas Engelbrecht, MD St. Louis, MO 20461	1	2	1	3	4 (1.0%)
S16536 *	David W. Faber, MD Salt Lake City, UT 19298	1	1	1	2	3 (0.8%)
S16537	Joseph Fan, MD Loma Linda, CA 16092	0	1	1	2	2 (0.5%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab 0.3 mg N=140	Ranibizumab 0.5 mg N=140	Ranibizumab Pooled N=280	All Subjects N=423
S15464 *	Leonard Feiner, MD Teaneck, NJ 19299	5	6	3	9	14 (3.6%)
S18904 *	Robert Feldman, MD Altamonte Springs, FL 05498	1	0	1	1	2 (0.5%)
S19699 *	Gregory Fox, MD Shawnee Mission, KS 20012	1	1	2	3	4 (1.0%)
S22018	Scott Foxman, MD Northfield, NJ 17920	0	0	1	1	1 (0.3%)
S19928 *	Ronald Frenkel, MD Stuart, FL 20722	1	0	0	0	1 (0.3%)
S20360 *	Ron Gallemore, MD Torrance, CA 21068	0	0	1	1	1 (0.3%)
S16538	Enrique Garcia-Valenzuela, MD Arlington Heights, IL 19339	0	0	1	1	1 (0.3%)
S15871	Louis Glazer, MD Grand Rapids, MI 13959	3	2	2	4	7 (1.8%)
S15958	Bernard Godley, MD Galveston, TX 13730	1	0	0	0	1 (0.3%)
S16530 *	Alan Gordon, MD Phoenix, AZ 16727	2	3	1	4	6 (1.5%)
S15913 *	Ernest Guillet, MD Rochester, NY 19471	2	3	4	7	9 (2.3%)
S16788 *	Sunil Gupta, MD Pensacola, FL 19948	0	0	1	1	1 (0.3%)
S15729	Darin Haivala, MD Oklahoma City, OK 19404	0	0	1	1	1 (0.3%)
S15469 *	Seenu Hariprasad, MD Chicago, IL 13257	0	1	1	2	2 (0.5%)
S15872 *	Yu-Guang He, MD Dallas, TX 19343	1	1	1	2	3 (0.8%)
S16564 *	Jeffrey S. Heier, MD Boston, MA 10018	3	3	4	7	10 (2.6%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab 0.3 mg N=140	Ranibizumab 0.5 mg N=140	Ranibizumab Pooled N=280	All Subjects N=423
S15736 *	Deborah Hoffert, MD Bangor, ME 19407	1	1	1	2	3 (0.8%)
S15470 S17723 *	John Hoskins, MD Knoxville, TN 19301	3	2	2	4	7 (1.8%)
S22229	John Huang, MD New Haven, CT 21622	1	0	0	0	1 (0.3%)
S15915 *	Baker Hubbard, MD Atlanta, GA 14235	1	1	1	2	3 (0.8%)
S15472 *	Cameron Javid, MD [2] Leonard Joffe, MD Tucson, AZ 22054	1	2	1	3	4 (1.0%)
S16542 *	Robert Johnson, MD San Francisco, CA 10019	1	0	1	1	2 (0.5%)
S15754 *	Randy Katz, MD Boynton Beach, FL 14008	1	1	1	2	3 (0.8%)
S16559 *	Alan Kimura, MD Denver, CO 19344	1	1	1	2	3 (0.8%)
S15878	Erik Kruger, MD Kingston, PA 19100	2	1	1	2	4 (1.0%)
S15880 *	S. Young Lee, MD Abilene, TX 19345	1	1	4	5	6 (1.5%)
S15479 *	Nicholas Leonardy, MD Toledo, OH 19303	1	1	1	2	3 (0.8%)
S15881 *	Eugene Lit, MD Oakland, CA 19055	2	3	2	5	7 (1.8%)
S18795 *	Louis Lobes, MD Pittsburgh, PA 09771	1	1	1	2	3 (0.8%)
S15882 *	Everett Madson, MD Omaha, NE 19346	1	0	0	0	1 (0.3%)
S15481 *	Naresh Mandava, MD Aurora, CO 17911	0	1	0	1	1 (0.3%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S15883 *	Dennis Marcus, MD Augusta, GA 13897	1	1	1	2	3 (0.8%)
S20590	Jose Martinez, MD Austin, TX 13866	2	2	1	3	5 (1.3%)
S15884 *	Mark Michels, MD, PA Palm Beach, FL 13872	2	2	1	3	5 (1.3%)
S15885 *	Robert Mittra, MD Edina, MN 16103	1	1	0	1	2 (0.5%)
S15933 *	George Novalis, MD Tucson, AZ 19483	2	2	1	3	5 (1.3%)
S15487	John Anthony Parchue, MD Fort Worth, TX 13628	1	0	1	1	2 (0.5%)
S16544 *	Arun Patel, MD Sacramento, CA 19429	2	2	3	5	7 (1.8%)
S16546 *	Matthew D. Paul, MD Danbury, CT 13506	0	1	0	1	1 (0.3%)
S16548 *	Jay Prensky, MD Camp Hill, PA 13505	1	1	1	2	3 (0.8%)
S16550	Carl Regillo, MD Philadelphia, PA 14609	1	2	2	4	5 (1.3%)
S15491	Adam Rogers, MD Boston, MA 19306	0	1	0	1	1 (0.3%)
S16551 *	Krista Rosenberg, MD Fort Lauderdale, FL 19677	2	2	1	3	5 (1.3%)
S15492 S18006 *	Daniel Roth, MD New Brunswick, NJ 19307	4	2	3	5	9 (2.3%)
S16315 *	David Saperstein, MD Seattle, WA 17922	1	1	1	2	3 (0.8%)
S16469 *	Todd Schneiderman, MD Silverdale, WA 14198	0	1	1	2	2 (0.5%)
S16556 *	Jerry Sebag, MD Huntington Beach, CA 13465	1	1	1	2	3 (0.8%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab			All Subjects N=423
			0.3 mg N=140	0.5 mg N=140	Pooled N=280	
S16557 *	Michael Singer, MD San Antonio, TX 13525	1	2	2	4	5 (1.3%)
S18767	Rishi Singh, MD Cleveland, OH 20446	5	5	4	9	14 (3.6%)
S16558 *	Brian Sippy, MD Missoula, MT 19316	1	1	1	2	3 (0.8%)
S15899 *	Allen Thach, MD Las Vegas, NV 11295	3	2	1	3	6 (1.5%)
S16560 *	Michael Tolentino, MD Winter Haven, FL 19318	1	3	3	6	7 (1.8%)
S18820 *	David Tom, MD Hamden, CT 13998	1	0	1	1	2 (0.5%)
S16553 *	Robert Torti, MD Desoto, TX 17684	1	1	2	3	4 (1.0%)
S16992 *	Erik Tu, MD Baldwin Park, CA 20022	1	0	0	0	1 (0.3%)
S15504 *	Allen Verne, MD Walnut Creek, CA 19292	2	1	1	2	4 (1.0%)
S16554 *	Thierry Verstraeten, MD Pittsburgh, PA 13844	4	3	3	6	10 (2.6%)
S22198	Kenneth Wald, MD New York, NY 16107	1	0	1	1	2 (0.5%)
S15505 *	Joseph Walker, MD Fort Myers, FL 13787	3	2	2	4	7 (1.8%)
S15506 *	Paul Weishaar, MD Wichita, KS 19319	2	2	1	3	5 (1.3%)
S15507 *	Mark Wieland, MD Mountain View, CA 19320	1	0	1	1	2 (0.5%)
S15898 *	Matthew Wood, MD Lincoln, NE 19413	1	2	1	3	4 (1.0%)
S16555 *	William Wood, MD Lexington, KY 19322	1	2	2	4	5 (1.3%)

Site Number	Investigator Name Location Investigator Number	Sham N=143	Ranibizumab 0.3 mg N=140	Ranibizumab 0.5 mg N=140	Ranibizumab Pooled N=280	All Subjects N=423
S16314 *	John Wroblewski, MD Hagerstown, MD 19754	3	3	2	5	8 (2.0%)
S19310 *	Lucy Young, MD Boston, MA 20794	1	1	1	2	3 (0.8%)

Reviewer's Comments:
It is preferred that at least ten patients be randomized per treatment arm per clinical site to allow for an investigator interaction analysis.

Note that Dr. Bakri replaced Dr. McCannel and Dr. Javid replaced Dr. Joffe during the course of the study.

An inconsistency was noted in the Investigator listing, Appendix 16.1.4. In this Appendix, Dr. Desai (Detroit, MI) is listed as an investigator in Study FVF4166g. However, he is not listed as an investigator in Table 14.1/1 Subject Enrollment by Investigator. In this table, Dr. Ober (S17741) is listed as an investigator in Detroit, MI. Review of the case report form site S17741 lists Dr. Desai as the investigator.

Table 6.1.3.2-2
Analysis Populations

Analysis Population	Sham (N=130)	Ranibizumab 0.3 mg (N=132)	Ranibizumab 0.5 mg (N=130)
Randomized subjects (ITT)	130 (100%)	132 (100%)	130 (100%)
Per-protocol subjects	104 (80.0%)	118 (89.4%)	102 (78.5%)
Safety-evaluable subjects	129 (99.2%)	132 (100%)	129 (99.2%)
Pharmacokinetic-evaluable subjects	128 (98.5%0	130 (99.3%)	128 (98.5%)

Reviewer's Comment:
The analysis populations were similar in number across treatment groups.

Table 6.1.3.2-3
Subject Disposition and Reason for Discontinuation during the 6-Month Treatment Period (Randomized Subjects)

Status and Primary Reason for Discontinuation	Number (%) of Subjects		
	Sham (n=132)	Ranibizumab	
		0.3 mg (n=134)	0.5 mg (n=131)
Received study drug	129 (99.2%)	132 (100%)	129 (99.2%)
Completed study through Month 6	115 (88.5%)	129 (97.7%)	119 (91.5%)
Discontinued treatment [a] at or prior to Month 5	16 (12.3%)	4 (3.0%)	10 (7.7%)
Adverse event	5 (3.8%)	0	1 (0.8%)
Lost to follow-up	0	2 (1.5%)	1 (0.8%)
Physician's decision	4 (3.1%)	1 (0.8%)	4 (3.1%)
Subject's decision	6 (4.6%)	1 (0.8%)	4 (3.1%)
Subject's condition mandated other therapeutic intervention	1 (0.8%)	0	0
Discontinued study prior to Month 6	15 (11.5%)	3 (2.3%)	11 (8.5%)
Adverse event	5 (3.8%)	0	1 (0.8%)
Lost to follow-up	0	1 (0.8%)	2 (1.5%)
Physician's decision	5 (3.8%)	1 (0.8%)	4 (3.1%)
Subject's decision	5 (3.8%)	1 (0.8%)	4 (3.1%)

a Subjects could remain in the study after treatment discontinuation.

Reviewer's Comment:

Three hundred and sixty three subjects (92.6%) completed Month 6. At or prior to Month 5, more subjects discontinued the study from the sham group (12.3%) than either the ranibizumab 0.3 mg group (3.0%) or the ranibizumab 0.5 mg group (7.7%) prior to Month 6.

The number of subjects who discontinued from the 0.5-mg treatment group was similar to that in the sham group.

Table 6.1.3.2-4
Major Protocol Deviations during the 6-Month Treatment Period
Randomized Subjects

Deviation	Sham (N=130)	Ranibizumab	
		0.3 mg (N=132)	0.5 mg (N=130)
Any deviation	**26 (20.0%)**	**14 (10.6%)**	**28 (21.5%)**
Missing baseline or Month 6 visual acuity score for the study eye [a]	19 (14.6%)	9 (6.8%)	19 (14.6%)
Violation of study eligibility criterion that was not approved by the Sponsor	5 (3.8%)	2 (1.5%)	8 (6.2%)
Anti-VEGF usage during the study	1 (0.8%)	0	0
Concurrent daily use of oral corticosteroids to treat a chronic condition	0	1 (0.8%)	0
Concurrent treatment with injectable corticosteroids to treat a musculoskeletal condition	1 (0.8%)	1 (0.8%)	3 (2.3%)
Treatment assignment unmasked	2 (1.5%)	2 (1.5%)	2 (1.5%)

Note: Table counts include subjects with at least one deviation of the type specified.
a All subjects with this deviation had missing Month 6 visual acuity scores for the study eye.

Reviewer's Comments:
The most frequent protocol deviation was missing baseline or Month 6 visual acuity score for the study eye. This protocol deviation occurred twice as frequently in the sham and 0.5 mg treatment groups as in the 0.3 mg treatment group. The reason for this imbalance is not clear.

Table 6.1.3.2-5 Discontinued Subjects and Reason
Study FVF4166g

Study Site ID	Subject ID	Reason for Discontinuation	Study Day	Visual Acuity (Letters)	
				Day 0	Last
Sham Group					
S15832	30304	AE - Subject's condition mandated other therapeutic intervention -- worsening VA	92	46	22
S15836	36803	AE – Iris neovascularization	29	58	17
S15882	32501	Physician's Decision to Withdraw	22	69	62
S15884	32601	Subject's Decision	141	28	36
S15899	36301	Subject's Decision	126	33	32
S16527	38903	Subject's Decision	127	49	50
S16529	33203	Subject's Decision	108	58	60
S16564	34203	Subject's Decision	62	29	32
	34209	Physician's Decision to Withdraw		70	70
S18516	36702	AE – Worsening macular edema	50	37	39
S18820	40502	AE – Fall, left hip broken	146	29	27
S20590	41002	AE – Physician's Decision to Withdraw – Neovascularization of Angle	112	48	31
S20590	41004	Physician's Decision to Withdraw	99	38	44

Study Site ID	Subject ID	Reason for Discontinuation	Study Day	Visual Acuity (Letters)	
				Day 0	Last
S22198	41601	Physician's Decision to Withdraw	10	43	42
S22229	41701	AE – Hypertensive Retinopathy	38	20	43
0.3 mg Group					
S15861	34014	Subject's Decision	181	29	43
S15878	34903	AE – Myocardial infarction	36	67	83
S16544	35601	Lost to Follow-up	166	43	49
0.5 mg Group					
S15464	31501	Physician's Decision to Withdraw	49	40	44
S15880	30201	AE – Chest pain	122	56	61
S16534	37108	Physician's Decision to Withdraw – BCVA ineligible on Day 0		66	66
S16535	34807	Subject's Decision	127	42	54
S16548	33401	Subject's Decision	11	26	30
S16550	38002	Subject's Decision	16	50	55
S16557	36005	Subject's Decision	156	56	66
S16560	34602	Lost to follow-up	161	48	82
S17723	32901	Physician's Decision to Withdraw	36	22	35
S17973	35001	Physician's Decision to Withdraw – Subject with active malignancy, ineligible	3	26	30
S22198	41602	Lost to follow-up	134	60	66

Reviewer's Comments:
There were fewer treatment discontinuations in the 0.3 mg treatment group compared with the sham and 0.5 mg treatment groups. The reason for the imbalance is not clear.

6.1.4 Efficacy Findings

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.

6.1.4.1 Study FVF4165g

PRIMARY EFFICACY RESULTS

Table 6.1.4.1-1
Mean Change from Baseline in Visual Acuity in the Study Eye at Month 6
Randomized Subjects

Visual Acuity at Month 6	Sham n=132	Ranibizumab	
		0.3 mg n=134	0.5 mg n=131
Number of letters change from baseline			
Mean (SD)	7.3 (13.0)	16.6 (11.0)	18.3 (13.2)
95% CI for mean [a]	(5.1, 9.5)	(14.7, 18.5)	(16.0, 20.6)
Difference in LS means (vs. sham) [b]		9.4	10.6
95% CI of the difference [b]		(6.6, 12.2)	(7.6, 13.6)
p-value (vs. sham) [c]		<0.0001	<0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
a Derived from t-distributions;
b Based on pairwise ANOVA models adjusted for baseline visual acuity score (≤34, 35-54, ≥ 55 letters).

Reviewer's Comment: *At Month 6, there was a mean change from baseline in visual acuity of 16.6 and 18.3 letters in the 0.3 mg and 0.5 mg ranibizumab treatment groups compared to 7.3 letters in the sham treatment group. The treatment group differences were statistically significant but less than the 15 letter difference accepted as clinical significance.*

SENSITIVITY ANALYSES OF VISUAL ACUITY

Table 6.1.4.1-2
Mean Change from Baseline in Visual Acuity in the Study Eye at Month 6
Per-Protocol Subjects

Visual Acuity at Month 6	Sham n=109	Ranibizumab	
		0.3 mg n=111	0.5 mg n=106
Number of letters change from baseline			
Mean (SD)	8.1 (12.8)	17.0 (10.6)	19.7 (12.4)
95% CI for mean [a]	(5.6, 10.5)	(15.0, 19.0)	(17.3, 22.1)
Difference in means (vs. sham) [b]		9.0	11.7
95% CI of the difference [b]		(5.8, 12.1)	(8.3, 15.1)
p-value (vs. sham)		<0.0001	<0.0001

Note: The last-observation-carried-forward method was used to impute missing data.. **a** Derived from t-distributions; **b** Based on pairwise ANOVA models adjusted for baseline visual acuity score (≤34, 35-54, ≥ 55 letters).

Reviewer's Comment: *The statistically significant treatment group difference was preserved in the Per Protocol population, but the mean difference is still less than 15 letters.*

Table 6.1.4.1-3
Gain of ≥ 15 Letters from Baseline in Visual Acuity in the Study Eye at Month 6

Gain of ≥ 15 Letters from Baseline	Sham (n=132)	Ranibizumab	
		0.3 mg (n=134)	0.5 mg (n=131)
Randomized Subjects LOCF (Worst Outcome Imputation)			
N	132	134	131
Responders	36 (27.3%)	73 (54.5%)	78 (59.5%)
95% CI of the % [a]	(19.7%, 34.9%)	(46.0%, 62.9%)	(51.1%, 67.9%)
Difference in % (vs. Sham) [b]		27.2%	32.3%
95% CI of the difference [b]		(15.9%, 38.6%)	(20.9%, 43.6%)
Test for treatment difference			
p-value (vs. Sham) [c]		<0.0001	<0.0001
Per Protocol Subjects (Observed Data)			
N	109	111	106
Responders	33 (30.3%)	64 (57.7%)	69 (65.1%)
95% CI of the % [a]	(21.6%, 38.9%)	(48.5%, 66.8%)	(56.0%, 74.2%)
Difference in % (vs. Sham) [b]		27.4%	34.8%
95% CI of the difference [b]		(14.8%, 40.0%)	(22.3%, 47.3%)
Test for treatment difference			
p-value (vs. Sham) [c]		<0.0001	<0.0001

Note: Observed cases only. Strata were defined using baseline visual acuity score (≤34, 35-54, ≥ 55 letters)
a All tests are two-sided and based on pairwise models. CIs are based on normal approximation for percentages and differences in percentages. **b** Based on weighted estimates of percentages and differences in percentages are based on weighted average of observed estimates across strata using CMH weights. **c** Using Pearson chi-squared (unstratified) and CMH chi-squared (stratified)

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.

Table 6.1.4.1-4
Loss of < 15 Letters from Baseline in the Study Eye at Month 6

Loss of < 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Randomized Subjects LOCF			
N	132	134	131
Responders	126 (95.5%)	134 (100.0%)	129 (98.5%)
95% CI of the % [a]	(90.5%, 98.0%)	(97.4%, 100%)	(94.6%, 99.7%)
Difference in % (vs. Sham) [b]		4.5%	3.0%
95% CI of the difference [b]		(1.6%, 9.9%)	(-1.5%, 8.3%)
Test for treatment difference			
p-value (vs. Sham) [c]		0.0141	0.2815
Randomized Subjects (Observed Data)			
N	121	126	123
Responders	117 (96.7%)	126 (100.0%)	122 (99.2%)
95% CI of the % [d]	(92.2%, 98.9%)	(97.2%, 100.0%)	(96.0%, 100.0%)
Difference in % (vs. Sham) [e]		3.3%	2.5%
95% CI of the difference [e]		(0.3%, 8.3%)	(-1.6%, 7.6%)
Test for treatment difference			
p-value (vs. Sham) [c]		0.0561	0.2111

All tests are two sided and based on pairwise models. Weighted estimates of percentages and differences in percentages are based on weighted average of observed estimates across strata using CMH weights. Exact CIs for percentages are calculated using the Blyth-Still-Casella method. Exact CIs for difference in percentages are calculated by inverting the exact two-sided score test.

SECONDARY EFFICACY ENDPOINT RESULTS

OCT Endpoints

The two secondary endpoints based on OCT at Month 6 were considered separately from the other secondary endpoints because they support the mechanism of action behind the primary endpoint. Contingent upon statistical significance in the primary endpoint for a given ranibizumab dose group, the following endpoints will be tested using the Hochberg-Bonferroni procedure at an overall α level of 0.05:

- Proportion of subjects with a central foveal thickness of ≤ 250 µm, assessed on OCT, at 6 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months (defined as successful if the comparison at Month 6 is statistically significant)

For mean changes from baseline in central foveal thickness, the procedure used to determine the earliest timepoint with a statistically significant difference was performed for a given ranibizumab dose group if the above testing procedure declared the difference between that ranibizumab dose group and the control group at Month 6 statistically significant. Beginning at Month 5 and moving backward, the test for a treatment difference at each timepoint was performed at a significance level of 0.05. The procedure was stopped at a given timepoint if the p-value of that timepoint's test was greater than 0.05.

Table 6.1.4.1-5 Central Foveal Thickness in the Study Eye at Month 6 (Randomized Subjects)

Central Foveal Thickness at Month 6	Sham (n=132)	Ranibizumab 0.3 mg (n=134)	Ranibizumab 0.5 mg (n=131)
≤ 250 µm			
n (%)	60 (45.5%)	122 (91.0%)	111 (84.7%)
95% CI for the % [a]	(37.0%, 53.9%)	(86.2%, 95.9%)	(78.6%, 90.9%)
Difference in % (vs. Sham) [b]		45.5%	40.1%
95% CI of the difference [b]		(36.0%, 55.0%)	(29.9%, 50.2%)
p-value (vs. Sham) [c]		<0.0001	<0.0001
Change from baseline (µm)			
Mean (SD)	-157.7 (224.2)	-337.3 (224.4)	-345.2 (238.2)
95% CI for the mean [d]	(-196.3, -119.1)	(-375.6, -298.9)	(-386.4, -304.0)
Difference in % (vs. Sham) [e]		-148.7	-134.8
95% CI of the difference [e]		(-183.6, -113.8)	(-172.7, -96.8)
p-value (vs. Sham) [f]		<0.0001	<0.0001

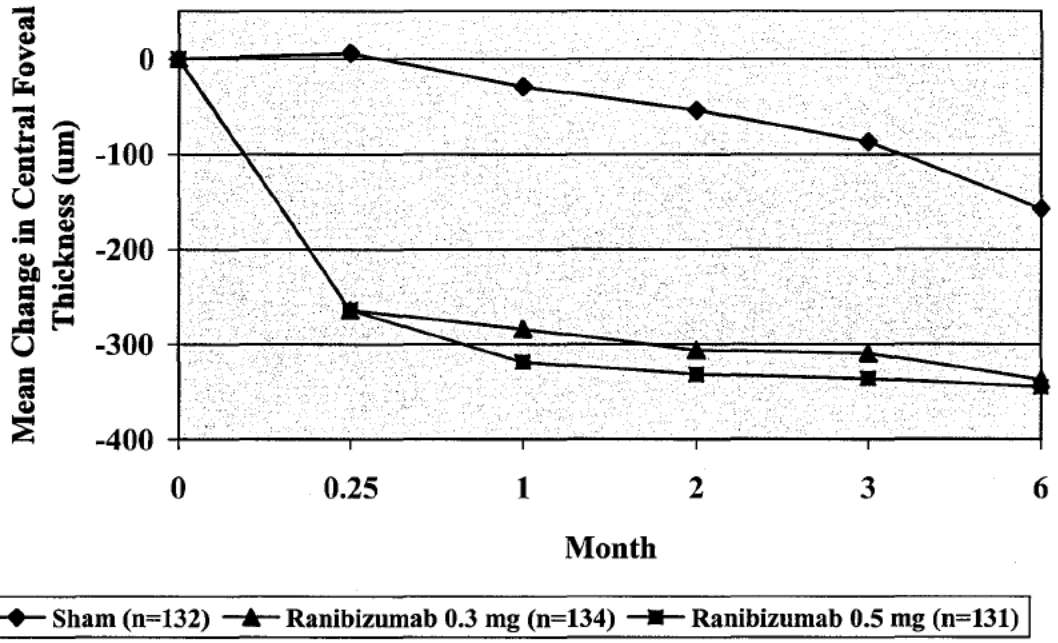
Note: Central foveal thickness was defined as the center point thickness. The last-observation-carried-forward method was used to impute missing data.
a By normal approximation
b Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters) using Cochran-Mantel-Haenszel weights.
c From Cochran-Mantel-Haenszel chi-square tests adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters).
d Derived from the t-distributions.
e Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters) and baseline value of central foveal thickness.

Reviewer's Comment:
The difference between each of the ranibizumab groups and the sham group in the proportion of subjects with a central foveal thickness of ≤ 250 μm at 6 months was statistically significant ($p<0.0001$).

The change from baseline in central foveal thickness by OCT in the study eye showed a treatment group difference for both ranibizumab groups compared with the sham group that was statistically significant at $p < 0.0001$ for each comparison.

Chart 6.1.4.1-1

Mean Change from Baseline in Central Foveal Thickness in the Study Eye Randomized Subjects



Reviewer's Comment:
The average decrease in central foveal thickness for the 0.3 mg and 0.5 mg ranibizumab-treated groups was 284.1 and 263.9 μm, respectively, one month after the first treatment. This average decrease was maintained for the duration of the study with maximal mean decrease in central foveal thickness of 337.3 and 345.2 μm respectively at 6 months. In contrast, the mean change in central foveal thickness for the sham group showed a slow decrease to 158 μm at 6 months.

The difference between each of the ranibizumab groups and the sham group in the mean change from baseline in central foveal thickness in the study eye at 6 months was statistically significant ($p<0.0001$).

Table 6.1.4.1-6 Proportion of Subjects Gaining ≥ 15 Letters and Proportion of Subjects Losing < 15 Letters in Visual Acuity from Baseline at Month 6 in the Study Eye (Randomized Subjects)

Visual Acuity at Month 6	Sham (n=132)	Ranibizumab 0.3 mg (n=134)	Ranibizumab 0.5 mg (n=131)
Gain of ≥ 15 letters from baseline			
Responders	38 (28.8%)	74 (55.2%)	80 (61.1%)
95% CI of the % [a]	(21.1%, 36.5%)	(46.8%, 63.6%)	(52.7%, 69.4%)
Difference in % (vs. Sham) [b]		26.8%	31.3%
95% CI of the difference [b]		(15.6%, 38.0%)	(20.1%, 42.6%)
p-value (vs. Sham) [c]		<0.0001	<0.0001
Loss of < 15 letters from baseline			
Responders	126 (95.5%)	134 (100%)	129 (98.5%)
95% CI of the % [d]	(90.5%, 98.0%)	(97.4%, 100%)	(94.6%, 99.7%)
Difference in % (vs. Sham) [e]		4.5%	3.0%
95% CI of the difference [e]		(15.9%, 38.6%)	(20.9%, 43.6%)
p-value (vs. Sham) [f]		0.0141	0.2815

Note: The last-observation-carried-forward method was used to impute missing data.
a By normal approximation.
b Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55) using Cochran-Mantel-Haenszel weights.
c From Cochran-Mantel-Haenszel chi-square tests adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55).
d Exact CI based on the Blyth-Still-Casella method
e Exact CI based on inverting the exact two-sided score test.
f Fisher's exact test.

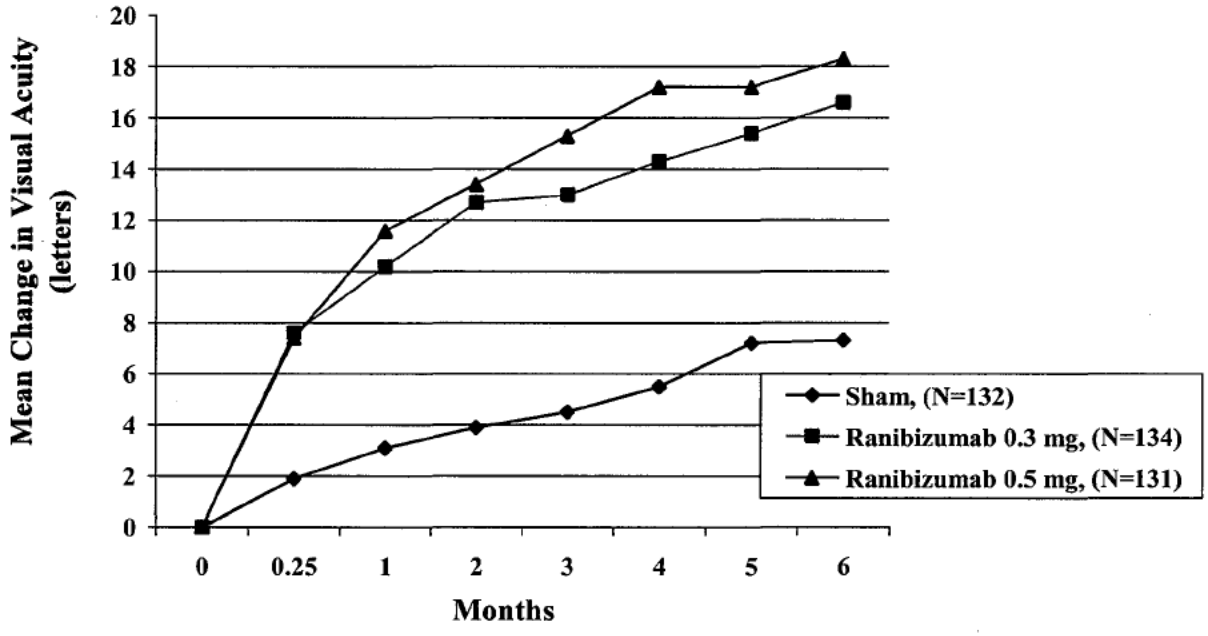
Reviewer's Comment:

The difference between each of the ranibizumab groups and the sham group in the proportion of subjects gaining ≥ 15 letters at 6 months was statistically significant (p< 0.0001).

The difference between the ranibizumab groups and the sham group in the proportion of subjects losing < 15 letters at 6 months was statistically significant for the 0.3 mg group versus the sham group (p=0.01) but was not statistically significant for the 0.5 mg group versus the sham group (p=0.28).

Chart 6.1.4.1-2

Mean Change from Baseline in Visual Acuity Score in the Study Eye
Randomized Subjects



	Baseline	Week 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Ranibizumab 0.5 mg (n=131)	0	7.4	11.6	13.4	15.3	17.2	17.2	18.3
Ranibizumab 0.3 mg (n=134)	0	7.6	10.2	12.7	13.0	14.3	15.4	16.6
Sham (n=132)	0	1.9	3.1	3.9	4.5	5.5	7.2	7.3

Reviewer's Comment:
The difference in mean change from baseline in visual acuity score between each of the ranibizumab groups and the sham group was statistically significant ($p<0.0001$) at Day 7 and at each monthly assessment.

Table 6.1.4.1-7 Mean Change from Baseline in the NEI VFQ-25 Near Activities and Distance Activities Subscale Scores at Month 6 (Randomized Subjects)

Change in NEI VFQ-25 Subscale Score at Month 6	Sham (n=129)	Ranibizumab	
		0.3 mg (n=133)	0.5 mg (n=130)
Near Activities			
Mean (SD)	7.3 (15.3)	12.1(17.3)	13.7 (18.0)
95% CI of the % [a]	(4.6, 10.0)	(9.1, 15.1)	(10.6, 16.8)
Difference in LS means (vs. Sham) [b]		4.1	6.4
95% CI of the difference [b]		(0.6, 7.6)	(3.0, 9.8)
p-value (vs. Sham) [c]		0.0214	0.0002
Distance Activities			
Mean (SD)	6.3 (15.0)	10.3 (17.2)	11.3 (16.6)
95% CI of the % [d]	(3.7, 8.9)	(7.3, 13.2)	(8.4, 14.2)
Difference in LS means (vs. Sham) [e]		3.8	5.1
95% CI of the difference [e]		(0.5, 7.0)	(2.0, 8.3)
p-value (vs. Sham) [f]		0.0248	0.0014

Note: The last-observation-carried-forward method was used to impute missing data.
a Derived from the t-distributions
b Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55) and baseline value of the corresponding endpoint.

Reviewer's Comment:
Though statistically significant treatment group differences were demonstrated, the external validity of the NEI VFQ-25 test has not yet been demonstrated.

The clinical significance of (b) (4) *in NEI VFQ score is not clear.* (b) (4)

> *"The NEI VFQ-25 instrument was developed with input from patients with a variety of ocular diseases and consists of a total of 12 subscale scores: general health, general vision, ocular pain, near activities, distance activities, vision-specific dependency, driving, color vision, and peripheral vision (Mangione et al. 1998, 2001).* (b) (4)
> (b) (4) (b) (4) (b) (4)

[redacted] (b) (4)
[redacted] (b) (4)
[redacted]

Selected Exploratory Efficacy Endpoint Results

Table 6.1.4.1-8
Proportion of Subjects with Snellen Equivalent of 20/40 or Better and Proportion of Subjects with Snellen Equivalent of 20/200 or Worse in the Study Eye at Month 6 (Randomized Subjects)

Visual Acuity at Month 6	Sham (n=132)	Ranibizumab 0.3 mg (n=134)	Ranibizumab 0.5 mg (n=131)
Snellen equivalent of 20/40 or better			
Responders	55 (41.7%)	91 (67.9%)	85 (64.9%)
95% CI of the % [a]	(33.3%, 50.1%)	(60.0%, 75.8%)	(56.7%, 73.1%)
Difference in % (vs. Sham) [b]		25.4%	24.7%
95% CI of the difference [b]		(15.1%, 35.7%)	(14.1%, 35.4%)
p-value (vs. Sham) [c]		<0.0001	<0.0001
Snellen equivalent of 20/200 or worse			
Responders	12 (9.1%)	2 (1.5%)	1 (0.8%)
95% CI of the % [d]	(5.2%, 15.2%)	(0.3%, 5.3%)	(0%, 3.8%)
Difference in % (vs. Sham) [e]		-7.6%	-8.3%
95% CI of the difference [e]		(-14.0%, -2.5%)	(-14.6%, -3.4%)
p-value (vs. Sham) [f]		0.0057	0.0027

Note: The last-observation-carried-forward method was used to impute missing data.
a By normal approximation
b Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters) using Cochran-Mantel-Haenszel weights.
c From Cochran-Mantel-Haenszel chi-square tests adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters).
d Exact CI based on the Blyth-Still-Casella method.
e Exact CI based on inverting the exact two-sided score test.
f Fisher's exact test

Reviewer's Comment:
At 6 months, 42% of patients in the sham group and 68% of patients in the 0.3mg, and 65% in the 0.5 mg ranibizumab treated groups had visual acuity of 20/40 or better (p<0.0001). Additionally, there were statistically significant differences in the proportion of patients with Snellen equivalent of 20/200 or worse at 6 months between the sham treated group (9%) and ranibizumab treated groups (2% in the 0.3 mg group and 1% in the 0.5 mg group).

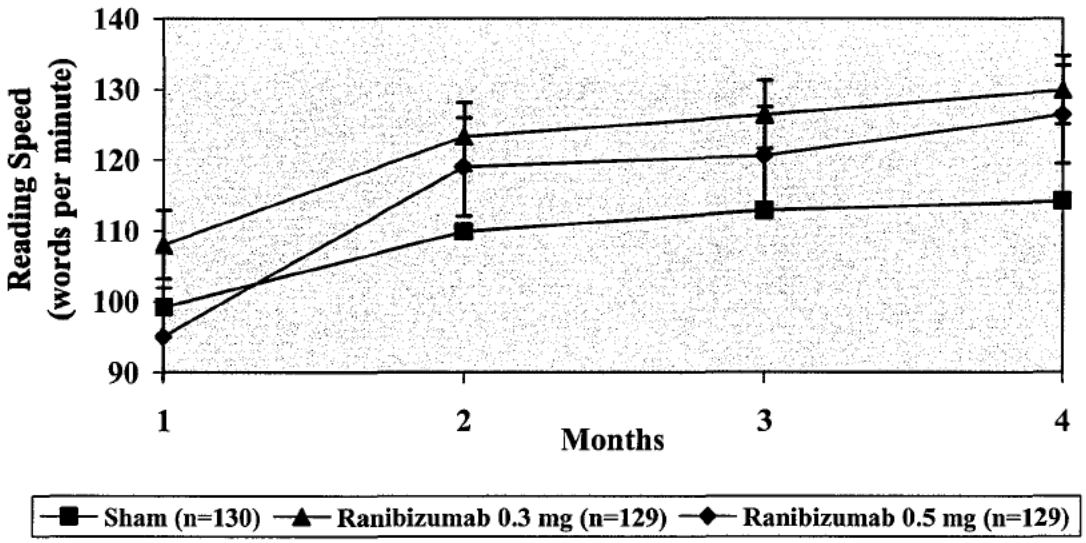
Reading Speed

Reading speed was measured by the number of correctly read words per minute on the reading speed test. The average reading speed in the study eye at baseline was 99.2, 108.0, and 95.0 words per minute for the sham, 0.3 mg, and 0.5 mg groups, respectively.

The applicant calculated the correlation between the change from baseline in study eye reading speed and the change from baseline in study eye visual acuity at Month 6 was 0.25 (95% CI: 0.15 to 0.34). The correlation between the change from baseline in study eye reading speed and the change from baseline in the NEI VFQ-25 near activities subscale at Month 6 was 0.12 (95% CI: 0.02 to 0.21).

Chart 6.1.4.1-3

Reading Speed in the Study Eye (Randomized Subjects)



Note: The last-observation carried forward method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.

Reviewer's Comment:
The mean reading speed at 6 months in the ranibizumab treated groups were 130 and 126 words per minute for the 0.3 mg and 0.5 mg groups compared with 114 words per minute in the sham group.

(b) (4) (b) (4)

Table 6.1.4.1-9
Subgroup Analysis of Primary Efficacy Variable at Month 6 by Baseline Visual Acuity (Randomized Subjects)

Number of BCVA Letters Change from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Baseline VA ≤ 34 Letters			
N	9	9	13
n (SD)	13.6 (14.7)	28.8 (12.5)	30.7 (8.0)
95% CI for Mean	(2.3, 24.9)	(19.2, 38.4)	(25.9, 35.5)
Difference in Means (vs. Sham)		15.2	17.1
p-value (vs. Sham)		0.03081	0.0021
Baseline VA 35 to 54 Letters			
N	50	48	49
n (SD)	8.9 (13.9)	19.6 (12.0)	21.8 (13.9)
95% CI for Mean	(5.0, 12.9)	(16.1, 23.1)	(17.8, 25.8)
Difference in Means (vs. Sham)		10.6	12.9
p-value (vs. Sham)		0.0001	<0.0001
Baseline VA ≥ 55 Letters			
N	73	77	69
n (SD)	5.4 (11.9)	13.3 (8.6)	13.4 (11.2)
95% CI for Mean	(2.6, 8.2)	(11.3, 15.2)	(10.8, 16.1)
Difference in Means (vs. Sham)		7.9	8.0
p-value (vs. Sham)		<0.0001	<0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
All tests are two-sided and based on pairwise models. CIs are based on normal approximation for percentages and differences in percentages,and on t-distribution for means and differences in means.

Table 6.1.4.1-10
Subgroup Analysis of Gain of ≥ 15 Letters from Baseline at Month 6
by Baseline Visual Acuity
(Randomized Subjects)

Gain of ≥ 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Baseline VA ≤ 34 Letters			
N	9	9	13
n (%)	3 (33.3%)	7 (77.8%)	13 (100.0%)
95% CI for Percentage	(2.5%, 64.1%)	(50.6%, 100.0%)	(100.0%, 100.0%)
Difference in % (vs. sham)		44.4%	66.7%
p-value (vs. sham)		0.0578	0.0006
Baseline VA 35 to 54 Letters			
N	50	48	49
n (%)	18 (36.0%)	32 (66.7%)	31 (63.3%)
95% CI for Percentage	(22.7%, 49.3%)	53.3%, 80.0%)	(49.8%, 76.8%)
Difference in % (vs. sham)		30.7%	27.3%
p-value (vs. sham)		0.0024	0.0067
Baseline VA ≥ 55 Letters			
N	73	77	69
n (%)	17 (23.3%)	35 (45.5%)	36 (52.2%)
95% CI for Percentage	(13.6%, 33.0%)	(34.3%, 56.6%)	(40.4%, 64.0%)
Difference in % (vs. sham)		22.2%	28.9%
p-value (vs. sham)		0.0044	0.0004

Note: The last-observation-carried-forward method was used to impute missing data.
All tests are two-sided and based on pairwise models. CIs are based on normal approximation for percentages and differences in percentages, and on t-distribution for means and differences in means. p values are from the Pearson Chi-squared (Unstratified)

Reviewer's Comment:

The number of evaluable subjects in several groups was very small making meaningful comparisons difficult. There were no differences seen in subgroup analyses based on age>65, age>75, gender, baseline foveal thickness or baseline visual acuity.

6.1.4.2 Study FVF4166g

PRIMARY EFFICACY RESULTS

Table 6.1.4.2-1
Mean Change from Baseline in Visual Acuity in the Study Eye at Month 6
Randomized Subjects

Visual Acuity at Month 6	Sham n=130	Ranibizumab	
		0.3 mg n=132	0.5 mg n=130
Number of letters change from baseline			
Mean (SD)	0.8 (16.2)	12.7 (15.9)	14.9 (13.2)
95% CI for mean [a]	(-2.0,3.6)	(9.9, 15.4)	(12.6, 17.2)
Difference in LS means (vs. sham) [b]		11.5	13.8
95% CI of the difference [b]		(7.7, 15.3)	(10.3, 17.4)
p-value (vs. sham) [e]		<0.0001	<0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
a Derived from t-distributions; **b** Based on pairwise ANOVA models adjusted for baseline visual acuity score (≤34, 35-54, ≥ 55 letters).

Reviewer's Comment:

At Month 6, there was a mean change from baseline in visual acuity of 12.7 and 14.9 letters in the 0.3 mg and 0.5 mg ranibizumab treatment groups compared to 0.8 letters in the sham treatment group. The treatment group differences were statistically significant (p<0.0001) but less than the 15 letter difference accepted as clinically significant.

SENSITIVITY ANALYSES OF VISUAL ACUITY

Table 6.1.4.2-2
Mean Change from Baseline in Visual Acuity in the Study Eye at Month 6 (Observed Data) Per-Protocol Subjects

Visual Acuity at Month 6	Sham n=104	Ranibizumab	
		0.3 mg n=118	0.5 mg n=102
Number of letters change from baseline			
Mean (SD)	2.4 (15.7)	12.6 (16.1)	15.1 (13.4)
95% CI for mean [a]	(-0.7, 5.4)	(9.7, 15.5)	(12.5, 17.8)
Difference in means (vs. sham) [a]		10.2	12.7
95% CI of the difference [b]		(6.0, 14.4)	(8.7, 16.8)
p-value (vs. sham)		<0.0001	<0.0001

All tests are two-sided and based on pairwise models. Weighted estimates of percentages and difference in percentages are based on weighted average of observed estimates across strata using CMH weights.
a CIs are based on t distribution for means and differences in means;

Reviewer's Comment:

The treatment group differences in mean change from baseline in visual acuity at Month 6 was preserved in the Per Protocol population with 12.6 and 15.1 letters in the 0.3 mg and 0.5 mg ranibizumab treatment groups compared to 2.4 letters in the sham treatment group. The treatment group differences were statistically significant ($p<0.0001$) but less than the 15 letter difference accepted as clinically significant.

Table 6.1.4.2-3
Gain of ≥ 15 Letters from Baseline in the Study Eye at Month 6

Gain of ≥ 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Randomized Subjects LOCF (Worst Outcome Imputation)			
N	130	132	130
Responders	21 (16.2%)	571 (43.2%)	56 (43.1%)
95% CI of the % [a]	(9.8%, 22.5%)	(34.7%, 51.6%)	(34.6%, 51.6%)
Difference in % (vs. Sham) [b]		27.0%	26.9%
95% CI of the difference [b]		(16.5%, 37.6%)	(16.3%, 37.5%)
Test for treatment difference			
p-value (vs. Sham) [c]		<0.0001	<0.0001
Per Protocol Subjects (Observed Data)			
N	104	118	102
Responders	21 (20.2%)	56 (47.5%)	53 (52.0%)
95% CI of the % [a]	(12.5%, 27.9%)	(38.4%, 56.5%)	(42.3%, 61.7%)
Difference in % (vs. Sham) [b]		27.3%	31.8%
95% CI of the difference [b]		(15.4%, 39.1%)	(19.4%, 44.2%)
Test for treatment difference			
p-value (vs. Sham) [c]		<0.0001	<0.0001

Note: Strata were defined using baseline visual acuity score (≤34, 35-54, ≥ 55 letters)
a All tests are two-sided and based on pairwise models. CIs are based on normal approximation for percentages and differences in percentages and on t-distribution for means and differences in means. Least square means (LS means), differences in LS means, and their CIs are from the ANOVA (stratified) model.

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.

Table 6.1.4.2-4
Loss of < 15 Letters from Baseline in the Study Eye at Month 6

Loss of < 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Randomized Subjects LOCF (Worst Outcome Imputation)			
N	130	132	130
Responders	97 (74.6%)	118 (89.4%)	109 (83.8%)
95% CI of the %	(67.1%, 82.1%)	(84.1%, 94.6%)	(77.5%, 90.2%)
Difference in % (vs. Sham)		14.8%	9.2%
95% CI of the difference		(5.6%, 23.9%)	(-0.6%, 19.0%)
Test for treatment difference			
p-value (vs. Sham)		0.0019	0.0654
Per Protocol Subjects (Observed Data)			
N	104	118	102
Responders	91 (87.5%)	113 (95.8%)	100 (98.0%)
95% CI of the %	(81.1%, 93.9%)	(92.1%, 99.4%)	(95.3%, 100.0%)
Difference in % (vs. Sham)		8.3%	10.5%
95% CI of the difference		(0.9%, 15.6%)	(3.6%, 17.4%)
Test for treatment difference			
p-value (vs. Sham)		0.0313	0.0046

Note: Strata were defined using baseline visual acuity score (≤34, 35-54, ≥ 55 letters)
All tests are two-sided and based on pairwise models. Weighted estimates of percentages and differences in percentages are based on weighted average of observed estimates across strata using CMH weights. CIs are based on normal approximation for percentages and differences in percentages.

Reviewer's Comment:

The difference between the ranibizumab groups and the sham group in the proportion of subjects losing < 15 letters at 6 months was marginally statistically significant for the 0.5 mg group versus the sham group in the Randomized - worst outcome imputation (p=0.0654) and the Per Protocol subjects (p=0.0046), uncorrected for multiple comparisons.

SECONDARY EFFICACY ENDPOINT RESULTS

Table 6.1.4.2-5 Proportion of Subjects Gaining ≥ 15 Letters and Proportion of Subjects Losing < 15 Letters in Visual Acuity from Baseline at Month 6 in the Study Eye (Randomized Subjects)

Visual Acuity at Month 6	Sham (n=130)	Ranibizumab 0.3 mg (n=132)	Ranibizumab 0.5 mg (n=130)
Gain of ≥ 15 letters from baseline			
Responders	22 (16.9%)	61 (46.2%)	62 (47.7%)
95% CI of the % [a]	(10.5%, 23.4%)	(37.7%, 54.7%)	(39.1%, 56.3%)
Difference in % (vs. Sham) [b]		29.3%	30.3%
95% CI of the difference [b]		(18.8%, 39.7%)	(19.6%, 40.9%)
p-value (vs. Sham) [c]		<0.0001	<0.0001
Loss of < 15 letters from baseline			
Responders	110 (84.6%)	127 (96.2%)	128 (98.5%)
95% CI of the % [d]	(78.4%, 90.8%)	(93.0%, 99.5%)	(96.3%, 100%)
Difference in % (vs. Sham) [e]		11.3%	13.6%
95% CI of the difference [e]		(4.3%, 18.2%)	(7.2%, 20.1%)
p-value (vs. Sham) [f]		0.0019	<0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
a By normal approximation.
b Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55) using Cochran-Mantel-Haenszel weights.
c From Cochran-Mantel-Haenszel chi-square tests adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55).

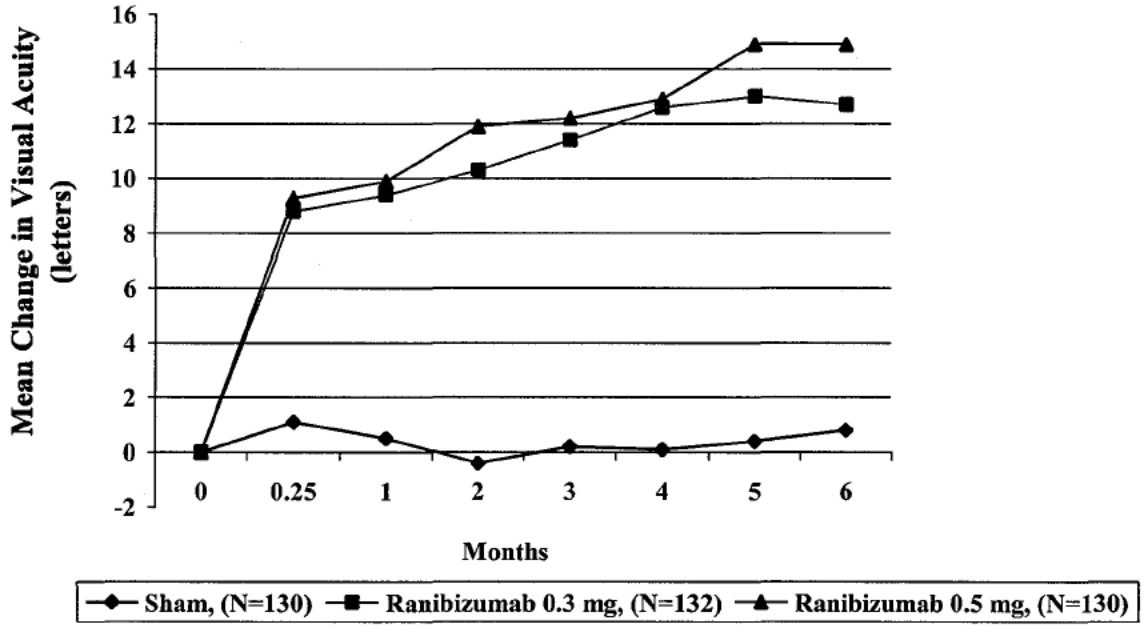
Reviewer's Comment:

The difference between each of the ranibizumab groups and the sham group in the proportion of subjects gaining ≥ 15 letters at 6 months was statistically significant (p< 0.0001).

The difference between the ranibizumab groups and the sham group in the proportion of subjects losing < 15 letters at 6 months was statistically significant for the 0.3 mg group versus the sham group (p=0.0019) and the 0.5 mg group versus the sham group (p< 0.0001).

Chart 6.1.4.2-1

Mean Change from Baseline in Visual Acuity Score in the Study Eye
Randomized Subjects



	Baseline	Week 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Ranibizumab 0.5 mg (n=130)	0	9.3	9.9	11.9	12.2	12.9	14.9	14.9
Ranibizumab 0.3 mg (n=132)	0	8.8	9.4	10.3	11.4	12.6	13.0	12.7
Sham (n=130)	0	1.1	0.5	-0.4	0.2	0.1	0.4	0.8

Reviewer's Comment:
The difference in mean change from baseline in visual acuity score between each of the ranibizumab groups and the sham group was statistically significant ($p<0.0001$) at Day 7 and at each monthly assessment.

Table 6.1.4.2-6 Central Foveal Thickness in the Study Eye at Month 6

(Randomized Subjects)

Central Foveal Thickness at Month 6	Sham (n=130)	Ranibizumab 0.3 mg (n=132)	Ranibizumab 0.5 mg (n=130)
≤ 250 µm			
n (%)	30 (23.1%)	99 (75.0%)	100 (76.9%)
95% CI for the % [a]	(15.8%, 30.3%)	(67.6%, 82.4%)	(69.7%, 84.2%)
Difference in % (vs. Sham) [b]		51.9%	54.0%
95% CI of the difference [b]		(41.6%, 62.3%)	(44.0%, 64.1%)
p-value (vs. Sham) [c]		<0.0001	<0.0001
Change from baseline (µm)			
n	129	131	130
Mean (SD)	-167.7 (308.4)	-433.7 (295.9)	-452.3 (257.6)
95% CI for the mean [d]	(-221.5, -114.0)	(-484.9, -382.6)	(-497.0, -407.6)
Difference in % (vs. Sham) [e]		-272.2	-283.8
95% CI of the difference [e]		(-329.9, -214.5)	(-337.8, -229.8)
p-value (vs. Sham) [f]		<0.0001	<0.0001

Note: Central foveal thickness was defined as the center point thickness. The last-observation-carried-forward method was used to impute missing data.

a By normal approximation

b Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters) using Cochran-Mantel-Haenszel weights.

c From Cochran-Mantel-Haenszel chi-square tests adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters).

d Derived from the t-distributions.

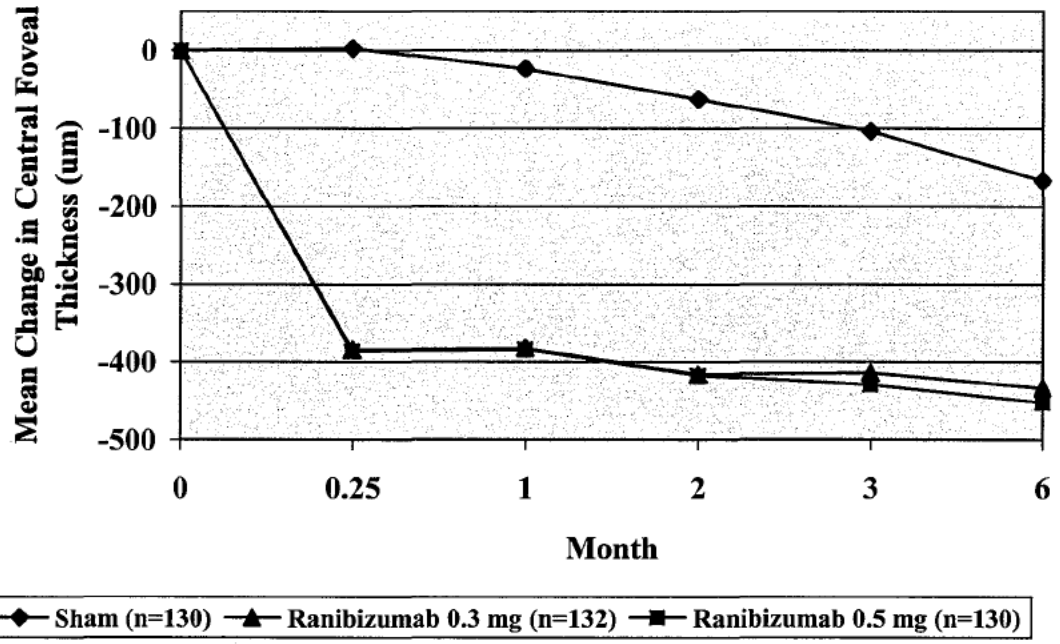
e Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters) and baseline value of central foveal thickness.

Reviewer's Comment:

At the Month 6 timepoint, 75% of subjects in the 0.3-mg group and 77% of subjects in the 0.5 mg group had a central foveal thickness of ≤ 250 µm compared to 23% in the sham group (p<0.0001).

Chart 6.1.4.2-2

Mean Change from Baseline in Central Foveal Thickness in the Study Eye Randomized Subjects



Note: Central foveal thickness was defined as the center point thickness. The last-observation-carried-forward method was used to impute missing data.

Reviewer's Comment:

The average decrease in central foveal thickness for the 0.3 mg and 0.5 mg ranibizumab-treated groups was 385 and 387 μm, respectively, one week after the first treatment. This average decrease was maintained through Month 6 with mean decrease in central foveal thickness of 434 and 452 μm for the 0.3-mg and 0.5-mg groups respectively. In contrast, the mean change in central foveal thickness in the sham group showed a gradual decrease leading to a maximal decrease of 168 μm at 6 months.

The difference between each of the ranibizumab groups and the sham group in the mean change from baseline in central foveal thickness in the study eye at 6 months was statistically significant ($p<0.0001$).

Table 6.1.4.2-7 Mean Change from Baseline in the NEI VFQ-25 Near Activities and Distance Activities Subscale Scores at Month 6 (Randomized Subjects)

Change in NEI VFQ-25 Subscale Score at Month 6	Sham (n=127)	Ranibizumab	
		0.3 mg (n=130)	0.5 mg (n=128)
Near Activities			
Responders	5.1 (17.1)	10.2(17.4)	9.3 (18.1)
95% CI of the % [a]	(2.1, 8.1)	(7.1, 13.2)	(6.1, 12.5)
Difference in LS means (vs. Sham) [b]		5.8	4.9
95% CI of the difference [b]		(2.1, 9.4)	(1.2, 8.6)
p-value (vs. Sham) [c]		0.0019	0.0099
Distance Activities			
Responders	2.8 (15.6)	8.9 (13.7)	6.7 (16.3)
95% CI of the % [d]	(0.0, 5.5)	(6.5, 11.2)	(3.8, 9.5)
Difference in LS means (vs. Sham) [e]		6.3	4.1
95% CI of the difference [e]		(3.1, 9.5)	(0.7, 7.6)
p-value (vs. Sham) [f]		0.0002	0.0199

Note: The last-observation-carried-forward method was used to impute missing data.
a Derived from the t-distributions
b Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55) and baseline value of the corresponding endpoint.

Reviewer's Comment:
Though statistically significant treatment group differences were demonstrated, the external validity of the NEI VFQ-25 test has not yet been proven. The clinical significance of the findings are unclear.

The applicant defined (b) (4) *in NEI VFQ-25 score as a clinically relevant response. Since this magnitude of change was observed in the sham group as well, the clinical relevance of this responder definition is questionable.*

Selected Exploratory Efficacy Endpoint Results

Table 6.1.4.2-8
Proportion of Subjects with Snellen Equivalent of 20/70 or Better and Proportion of Subjects with Snellen Equivalent of 20/200 or Worse in the Study Eye at Month 6 (Randomized Subjects)

Visual Acuity at Month 6	Sham (n=130)	Ranibizumab 0.3 mg (n=132)	Ranibizumab 0.5 mg (n=130)
Snellen equivalent of 20/70 or better			
Responders	53 (40.8%)	75 (56.8%)	82 (63.1%)
95% CI of the % [a]	(32.3%, 49.2%)	(48.4%, 65.3%)	(54.8%, 71.4%)
Difference in % (vs. Sham) [b]		18.3%	24.7%
95% CI of the difference [b]		(8.2%, 28.5%)	(14.9%, 34.5%)
p-value (vs. Sham) [c]		0.0007	<0.0001
Snellen equivalent of 20/200 or worse			
Responders	36 (27.7%)	20 (15.2%)	15 (11.5%)
95% CI of the % [a]	(20.0%, 35.4%)	(9.0%, 21.3%)	(6.0%, 17.0%)
Difference in % (vs. Sham) [b]		-14.4%	-17.6%
95% CI of the difference [b]		(-23.2%, -5.7%)	(-26.0%, -9.3%)
p-value (vs. Sham) [c]		0.0020	<0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
a By normal approximation
b Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters) using Cochran-Mantel-Haenszel weights.
c From Cochran-Mantel-Haenszel chi-square tests adjusted for baseline visual acuity score (≤ 34, 35-54, ≥ 55 letters).

Reviewer's Comment:

At 6 months, 40.8% of patients in the sham group and 57% and 63% of patients in the 0.3mg and 0.5 mg ranibizumab treated groups had visual acuity of 20/70 or better. These treatment group differences when compared with sham treatment were statistically significant for the 0.3-mg group (p=0.0007) and for the 0.5-mg group (p<0.0001).

Additionally, there were statistically significant differences in the proportion of patients with Snellen equivalent of 20/200 or worse at 6 months between the sham treated group (28%) and ranibizumab treated groups (15% in the 0.3 mg group and 63% in the 0.5 mg group).

Iris Neovascularization
Based on slitlamp examination, iris neovascularization was present in 4 subjects at baseline. A total of 15 subjects (9 [6.9%] in the sham group, 3 [2.3%] in the 0.3-mg group and 3[2.3%] in the 0.5-mg group), had iris neovascularization at any post-baseline timepoint at or prior to Month 6.

Rubeosis
Based on gonioscopic examinations, rubeosis in the anterior chamber angle was present in 5 subjects (2 subjects in the 0.3-mg group and 3 subjects in the 0.5-mg group) at baseline. Of the subjects without rubeosis in the anterior chamber angle at baseline, 12 subjects (10 [9.7%] in the sham group, 2 [1.9%] in the 0.3-mg group, and no subjects in the 0.5-mg group) had rubeosis develop in the anterior chamber angle at any post-baseline timepoint at or prior to Month 6.

Rubeosis at the pupillary margin was present in 10 subjects (2 subjects sham group, 6 subjects in the 0.3-mg group, and 2 subjects in the 0.5-mg group) at baseline. Of the subjects without rubeosis at the pupillary margin at baseline, 24 subjects (10 [9.9%] in the sham group, 7 [6.8%] in the 0.3-mg group, and 7 [6.7%] subjects in the 0.5-mg group) had rubeosis develop at the pupillary margin at any post-baseline timepoint at or prior to Month 6.

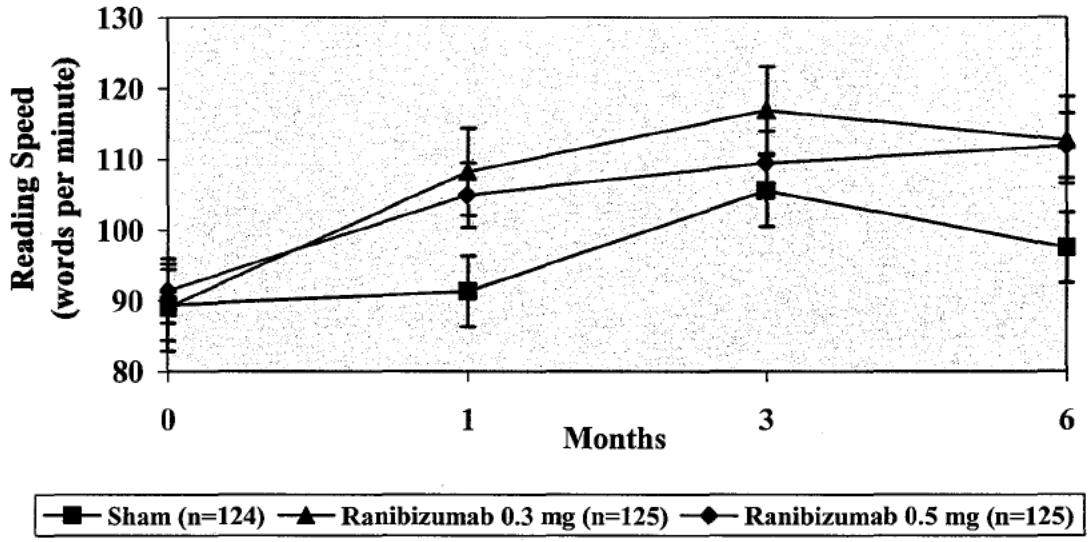
Scatter Photocoagulation
Based on the Concurrent Ocular Procedures CRF, scatter photocoagulation was received by 7 subjects (6 [4.6%] in the sham group, 1 [0.8%] in the 0.3-mg group and no subjects in the 0.5-mg group) at or prior to Month 6.

Reading Speed
Reading speed was measured by the number of correctly read words per minute on the reading speed test. The average reading speed in the study eye at baseline was 89.4, 89.0, and 91.4 words per minute for the sham, 0.3 mg, and 0.5 mg groups, respectively.

The applicant calculated the correlation between the change from baseline in study eye reading speed and the change from baseline in study eye visual acuity at Month 6 was 0.25 (95% CI: 0.15 to 0.34). The correlation between the change from baseline in study eye reading speed and the change from baseline in the NEI VFQ-25 near activities subscale at Month 6 was 0.12 (95% CI: 0.02 to 0.21).

Chart 6.1.4.2-3

**Reading Speed in the Study Eye
(Randomized Subjects)**



Note: The last-observation carried forward method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.

Reviewer's Comment:
The mean reading speed at 6 months was 113 and 112 words per minute in the ranibizumab 0.3 mg and 0.5 mg groups respectively compared with 98 words per minute in the sham group.

Table 6.1.4.2-9
Subgroup Analysis of Gain of ≥ 15 Letters from Baseline at Month 6 by Baseline Visual Acuity (Randomized Subjects)

Gain of ≥ 15 Letters from Baseline	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Baseline VA ≤ 34 Letters			
N	26	33	30
n (%)	5 (19.2%)	16 (48.5%)	16 (53.3%)
95% CI for Percentage	(4.1%, 34.4%)	(31.4%, 65.5%)	(35.5%, 71.2%)
Difference in % (vs. sham)		29.3%	34.1%
p-value (vs. sham)		0.0198	0.0086
Baseline VA 35 to 54 Letters			
N	49	46	50
n (%)	14 (28.6%)	26 (56.5%)	25 (50.0%)
95% CI for Percentage	(15.9%, 41.2%)	(42.2%, 70.8%)	(36.1%, 63.9%)
Difference in % (vs. sham)		28.0%	21.4%
p-value (vs. sham)		0.0058	0.0291
Baseline VA ≥ 55 Letters			
N	55	53	50
n (%)	3 (5.5%)	19 (35.8%)	21 (42.0%)
95% CI for Percentage	(0.0%, 11.5%)	(22.9%, 48.8%)	(28.3%, 55.7%)
Difference in % (vs. sham)		30.4%	36.5%
p-value (vs. sham)		<0.0001	<0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
All tests are two-sided and based on pairwise models. CIs are based on normal approximation for percentages and differences in percentages, and on t-distribution for means and differences in means. p values are from the Pearson Chi-squared (Unstratified)

6.1.5 Clinical Microbiology

This is not an antimicrobial. Not applicable.

6.1.6 Efficacy Conclusions

The two Phase 3 clinical trials demonstrate efficacy for the use of ranibizumab 0.5 mg for the treatment of macular edema following retinal vein occlusion.

The FVF4165g study enrolled patients with macular edema following branch retinal vein occlusion and demonstrated an approximately 11 letter treatment effect of ranibizumab 0.5-mg compared to sham treatment ($p < 0.0001$), for the primary efficacy endpoint, the mean change from baseline in visual acuity at Month 6 in subjects with branch retinal vein occlusion.

The results are replicated by the findings of the other submitted Phase 3 clinical trial, FVF4166g. The FVF4166g study demonstrates an approximately 14 letter treatment difference of ranibizumab 0.5-mg compared to sham treatment ($p < 0.0001$), for the primary efficacy endpoint, the mean change from baseline in visual acuity at Month 6 in subjects with central retinal vein occlusion.

7 INTEGRATED REVIEW OF SAFETY

This review of safety describes the safety profile of Lucentis (ranibizumab injection) for the treatment of macular edema following retinal vein occlusion (RVO). Data from Studies FVF4165g and FVF4166g, two pivotal Phase 3 studies in RVO, are included in this section.

7.1 Methods and Findings

7.1.1 Deaths

In Study FVF4165g, one death occurred during the 6-month treatment period. Subject 11009, a 78-year-old white male died of a cerebral hemorrhage on Study Day 177. This subject was in the 0.5-mg ranibizumab group, and the death occurred 26 days after his sixth treatment with study drug. This subject's medical history included a prior hemorrhagic cerebrovascular accident.

In Study FVF4166g, no deaths occurred during the 6-month treatment period. However, Subject 37301 in the sham group experienced a serious adverse event, gastric cancer, during the 6-month treatment period that resulted in the subject's death during the 6-month observation period of the study.

Reviewer's Comment:
The deaths were not considered to be related to therapy.

7.1.2 Other Serious Adverse Events

Table 7.1.2-1 Studies FVF4165g
Ocular Serious Adverse Events in the Study Eye during the 6 Month Treatment Period
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
Sham Group				
None				
0.3 mg Group				
S16541	12004	Retinal tear and retinal detachment	92	Dose held, Pneumatic retinopexy, cryotherapy
S16254	13203	Corneal abrasion	6	Medication
S16270	14902	Retinal ischemia Worsening hypertension	48 107	None Medication change
0.5 mg Group				
S16502	16307	Severe endophthalmitis	132	Vitreous tap, intravitreal Abx, etc.
S15706	17502	Worsening of branch retinal vein occlusion	64	

Table 7.1.2-2 Studies FVF4166g
Ocular Serious Adverse Events in the Study Eye during the 6 Month Treatment Period
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
Sham Group				
None				
0.3 mg Group				
S16530	30106	Worsening of macular edema	20	None
S15505	31106	Retinal vascular disorder (macular non-perfusion, partial retinal artery occlusion)	57	Dose held
S15464	31508	Severe corneal edema	120	Medication
S15898	35504	Progression of macular edema	92	None
0.5 mg Group				
S16534	37103	Retinal vascular occlusion	85	Dose held
S16560	34607	Unilateral blindness, iris neovascularization	93	None

Table 7.1.2-3 Studies FVF4165g
Ocular Serious Adverse Events in the Fellow Eye during the 6 Month Treatment Period
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
Sham Group				
None				
0.3 mg Group				
S15387	13701	Neovascular glaucoma	117	Laser – PRP, surgery
S15341	17602	30 letter loss in vision	151	None
0.5 mg Group				
S16389	15705	Gaze palsy	132	None

Table 7.1.2-2 Studies FVF4166g
Ocular Serious Adverse Events in the Fellow Eye during the 6 Month Treatment Period
Safety Evaluable Subjects

Study Site ID	Subject ID	Adverse Event	Day of Onset	Action Taken
Sham Group				
None				
0.3 mg Group				
S15899	36303	Central retinal vein occlusion, retinal disorder, retinal depigmentation, and maculopathy	102	None
0.5 mg Group				
S16560	34607	Central retinal vein occlusion	65	Dose held, triamcinolone injxn

A single case of endophthalmitis was reported in the 0.5 mg treatment group. The per injection rates of endophthalmitis and retinal detachment were 0.07%. There were no intraocular inflammation events which includes preferred terms of anterior chamber inflammation, hypopyon, iridocyclitis, iritis, uveitis, viral iritis, and vitritis.

Reviewer's Comment:
Sixteen subjects experienced at least one ocular serious adverse event in the study eye during the 6-month treatment period.

There were no serious adverse events during the first treatment year in the sham group.

Two subjects in Study FVF4166g which studied CRVO experienced an occurrence of CRVO in the fellow eye during the 6 month treatment period.

Table 7.1.2-2 Rate Per Injection of Ocular Serious Adverse Events in the Study Eye during the 6-Month Treatment Period Studies FVF4165g and FVF4166g Pooled

	Sham (n=260)	Ranibizumab	
		0.3 mg (n=266)	0.5 mg (n=259)
Total number of injections [a]	**1436**	**1534**	**1465**
Cataract traumatic	0	0	0
Endophthalmitis	0	0	1 (0.0683%)
Intraocular inflammation [b]	0	0	0
Retinal detachment	0	1 (0.0652%)	0

Note: Rate per injection was calculated as follows: (number of events/ total number of injections) x 100%.
a Intravitreal ranibizumab injections or sham injections.
b Includes the preferred terms of anterior chamber inflammation, hypopyon, iridocyclitis, iritis, uveitis, viral iritis, and vitritis.

Reviewer's Comment:
The per injection rate of ocular serious adverse events in the study eye were very small.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Refer to Tables 6.1.3.1-6 and 6.1.3.2-5 for listings of discontinued subjects and the reason for discontinuation.

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

	Study FVF4165g Number of Subjects			Study FVF4166g Number of Subjects		
	Sham n=132	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=131	Sham n=132	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=131
Received study drug	131 (99.2%)	134 (100%)	130 (99.2%)	129 (99.2%)	132 (100%)	129 (99.2%)
Completed study through Month 6	123 (93.2%)	128 (95.5%)	125 (95.4%)	115 (88.5%)	129 (97.7%)	119 (91.5%)
Discontinued treatment [a] prior to Month 5	9 (6.8%)	5 (3.7%)	5 (3.8%)	16 (12.3%)	4 (3.0%)	10 (7.7%)
Death	0	0	0	0	0	0
Adverse Event	0	0	2 (1.5%)	5 (3.8%)	0	1 (0.8%)
Lost to follow-up	0	1 (0.7%)	0	0	2 (1.5%)	1 (0.8%)
Physician's Decision	1 (0.8%)	1 (0.7%)	3 (2.3%)	4 (3.1%)	1 (0.8%)	4 (3.1%)
Subject's Decision	7 (5.3%)	3 (2.2%)	0	6 (4.6%)	1 (0.8%)	4 (3.1%)
Subject's condition mandated other therapeutic intervention	1 (0.8%)	0	0	1 (0.8%)	0	0
Discontinued study prior to Month 6	9 (6.8%)	6 (4.5%)	6 (4.6%)	15 (11.5%)	3 (2.3%)	11 (8.5%)
Death	0	0	1 (0.8%)	0	0	0
Adverse Event	0	0	1 (0.8%)	5 (3.8%)	0	1 (0.8%)
Lost to follow-up	0	1 (0.7%)	0	0	1 (0.8%)	2 (1.5%)
Physician's Decision	1 (0.8%)	1 (0.7%)	3 (2.3%)	5 (3.8%)	1 (0.8%)	4 (3.1%)
Subject's Decision	7 (5.3%)	4 (3.0%)	1 (0.8%)	5 (3.8%)	1 (0.8%)	4 (3.1%)
Subject's condition mandated other therapeutic intervention	1 (0.8%)	0	0	0	0	0

a Subjects could remain in the study after treatment discontinuation.

Reviewer's Comment:

In Study FVF4165g, the sham injection group had higher rates of study dropout and treatment discontinuation than in the ranibizumab groups. However, in Study FVF4166g, the sham and ranibizumab 0.5 mg groups had similar discontinuation rates.

The number of discontinuations was evenly distributed between adverse events, Physician Decision and Subject Decisions in the sham group. In the ranibizumab 0.5 mg group, they were predominantly due to Physician and Subject Decision.

7.1.3.2 Adverse events associated with dropouts

Table 7.1.3.2-2
Ocular Adverse Events That Led to Treatment Discontinuation during the 6- Month Treatment Period: Studies FVF4165g and FVF4166g Pooled

MedDRA Preferred Term	Sham (n=260)	Ranibizumab 0.3 mg (n=266)	Ranibizumab 0.5 mg (n=259)
Any adverse event	**5 (1.9%)**	**1 (0.4%)**	**1 (0.4%)**
Corneal edema	0	1 (0.4%)	0
Endophthalmitis	0	0	1 (0.4%)
Iris neovascularization	1 (0.4%)	0	0
Macular ischemia	1 (0.4%)	0	0
Macular edema	2 (0.8%)	0	0
Retinal vein occlusion	2 (0.8%)	0	0

Note: Table entries are number (%) of subjects with at least one adverse event of the type specified.

Table 7.1.3.2-3
Non-Ocular Adverse Events That Led to Treatment Discontinuation during the 6- Month Treatment Period: Studies FVF4165g and FVF4166g Pooled

MedDRA Preferred Term	Sham (n=260)	Ranibizumab 0.3 mg (n=266)	Ranibizumab 0.5 mg (n=259)
Any adverse event	**2 (0.8%)**	**2 (0.8%)**	**3 (1.2%)**
Arteriosclerosis coronary artery	0	0	1 (0.4%)
Cerebral hemorrhage	0	0	1 (0.4%)
Dementia Alzheimer's type	0	1 (0.4%)	0
Gastric cancer	1 (0.4%)	0	0
Herpes zoster oticus	0	0	1 (0.4%)
Hip fracture	1 (0.4%)	0	0
Myocardial infarction	0	1 (0.4%)	0

Note: Table entries are number (%) of subjects with at least one adverse event of the type specified.

Reviewer's Comment:
The percentage of subjects who experienced ocular and/or non-ocular adverse events which led to treatment discontinuation was less than 2%. More subjects in the sham group experienced ocular adverse events that led to treatment discontinuation. The number of non-ocular adverse events that led to treatment discontinuation was similar in all treatment groups.

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 6-Month Treatment Period: Studies FVF4165g and FVF4166g (Safety Evaluable Subjects)

MedDRA Preferred Term	Study FVF4165g			Study FVF4166g		
	Sham n=131	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=130	Sham n=129	Ranibizumab 0.3 mg n=132	Ranibizumab 0.5 mg n=129
Any adverse event	**1 (0.8%)**	**4 (3.0%)**	**5 (3.8%)**	**2 (1.6%)**	**2 (1.5%)**	**2 (1.6%)**
Arterial thromboembolic events						
Any adverse event	1 (0.8%)	0	3 (2.3%)	1 (0.8%)	2 (1.5%)	2 (1.6%)
Acute coronary syndrome	0	0	0	1 (0.8%)	0	0
Acute myocardial infarction	0	0	1 (0.8%)	0	1 (0.8%)	1 (0.8%)
Angina pectoris	0	0	0	0	0	1 (0.8%)
Angina unstable	0	0	1 (0.8%)	0	0	0
Cerebral hemorrhage	0	0	1 (0.8%)	0	0	0
Retinal artery occlusion	0	0	0	0	1 (0.8%)	0
Thalamus hemorrhage	1 (0.8%)	0	0	0	0	0
Transient ischemic attack	0	0	0	0	0	1 (0.8%)
Hypertension						
Any adverse event	0	2 (1.5%)	0	1 (0.8%)	0	0
Hypertension	0	2 (1.5%)	0	1 (0.8%)	0	0
Non-ocular hemorrhage						
Any adverse event	1 (0.8%)	2 (1.5%)	2 (1.5%)	0	0	0
Cerebral hemorrhage	0	0	1 (0.8%)	0	0	0
Intra-abdominal hematoma	0	1 (0.7%)	0	0	0	0
Post procedural hemorrhage	0	0	1 (0.8%)	0	0	0
Rectal hemorrhage	0	1 (0.7%)	0	0	0	0
Thalamus hemorrhage	1 (0.8%)	0	0	0	0	0
Other potentially associated events						
Any adverse event	0	0	1 (0.8%)	0	0	0
Intestinal perforation	0	0	1 (0.8%)	0	0	0

Note: Table counts include subjects with at least one adverse event of the type specified.

Reviewer's Comment:
Serious adverse events potentially related to systemic VEGF inhibition during the 6 month treatment period occurred at a rate of 1-4% in the ranibizumab-treated groups. In Study FVF4165g, there were more events in the ranibizumab-treated groups. In Study FVF4166g, the numbers of events were evenly distributed across all treatment groups.

Table 7.1.3.3-2 APTC Arterial Thromboembolic Events during the 6-Month Treatment Period: Studies FVF4165g and FVF4166g (Safety Evaluable Subjects)

Type of Adverse Event	Study FVF4165g			Study FVF4166g		
	Sham n=131	Ranibizumab 0.3 mg n=134	Ranibizumab 0.5 mg n=130	Sham n=129	Ranibizumab 0.3 mg n=132	Ranibizumab 0.5 mg N=129
Any event	**1 (0.8%)**	**0**	**2 (1.5%)**	**1 (0.8%)**	**1 (0.8%)**	**1 (0.8%)**
Nonfatal myocardial infarction	0	0	1 (0.8%)	1 (0.8%) [a]	1 (0.8%)	1 (0.8%)
Fatal cerebrovascular accident	0	0	1 (0.8%)	0	0	0
Nonfatal cerebrovascular accident	1 (0.8%)	0	0	0	0	0
Vascular death	0	0	1 (0.8%)	0	0	0
APTC event (vascular death, unknown cause death, non-fatal myocardial infarction, non-fatal cerebrovascular accident)	1 (0.8%)	0	2 (1.5%)	1 (0.8%)	1 (0.8%)	1 (0.8%)

Note: Arterial thromboembolic events, defined according to the Antiplatelet Trialists' Collaboration (APTC) classification (1994), are presented. 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.
a Reported as acute coronary syndrome.

Reviewer's Comment:
Applying the APTC classification to the serious adverse events, the overall frequency of events is less than 2% and similar across all treatment groups in both studies.

Table 7.1.3.3-3 Intraocular Inflammation in the Study Eye during the 6-Month Treatment Period Studies FVF4165g and FVF4166g: Safety Evaluable Subjects

MedDRA Preferred Terms	Study FVF4165g			Study FVF4166g		
	Sham N=131	Ranibizumab 0.3 mg N=134	Ranibizumab 0.5 mg N=130	Sham N=129	Ranibizumab 0.3 mg N=132	Ranibizumab 0.5 mg N=129
Any intraocular inflammation	**4 (3.1%)**	**2 (1.5%)**	**0**	**5 (3.9%)**	**3 (2.3%)**	**2 (1.6%)**
Iridocyclitis	0	1 (0.7%)	0	0	0	0
Iritis	4 (3.1%)	1 (0.7%)	0	3 (2.3%)	2 (1.5%)	2 (1.6%)
Uveitis	0	0	0	0	0	0
Vitritis	2 (1.6%)	1 (0.8%)	1 (0.8%)	0	0	0
Any serious intraocular inflammation	0	0	0	0	0	0

Reviewer's Comment:
There was a dose dependent relationship between ranibizumab and intraocular inflammation in the AMD studies not observed in the RVO studies. There is no obvious explanation for the difference.

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

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

Table 7.1.5.3-1
Adverse Events Occurring in ≥ 1 % of Patients during the 6-Month Treatment Period: Studies FVF4165g and Study FVF4166g Pooled
Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Sham N=260	Ranibizumab Pooled	
		0.3 mg N=266	0.5 mg N=259
Blood and Lymphatic System Disorders			
Anemia	3 (1.2%)	3 (1.1%)	3 (1.2%)
Cardiac Disorders			
Coronary artery disease	3 (1.2%)	1 (0.4%)	2 (0.8%)
Ear and Labyrinth Disorders			
Vertigo	7 (2.7%)	3 (1.1%)	1 (0.4%)
Eye Disorders			
Blepharitis	3 (1.2%)	3 (1.1%)	1 (0.4%)
Cataract	4 (1.5%)	3 (1.2%)	6 (2.3%)
Conjunctival hemorrhage	97 (37.3%)	137 (51.5%)	124 (47.9%)
Conjunctival hyperemia	1 (0.4%)	4 (1.5%)	1 (0.4%)
Conjunctivitis	0	0	3 (1.2%)
Corneal abrasion	4 (1.5%)	4 (1.5%)	1 (0.4%)
Diplopia	1(0.4%)	4 (1.5%)	2 (0.8%)
Drug administration error	4 (1.5%)	2 (0.8%)	1 (0.4%)
Dry Eye	7 (2.7%)	6 (2.3%)	7 (2.7%)
Eye discharge	3 (1.2%)	3 (1.1%)	6 (2.3%)
Eye irritation	16 (6.2%)	14 (5.3%)	17 (6.6%)
Eye pain	32 (12.3%)	44 (16.5%)	45 (17.4%)
Eye pruritus	6 (2.3%)	7 (2.6%)	3 (1.2%)
Eyelid edema	4 (1.5%)	2 (0.8%)	2 (0.8%)
Foreign body sensation in eyes	13 (5.0%)	10 (3.8%)	18 (6.9%)
Intraocular pressure increased	6 (2.3%)	18 (6.8%)	17 (6.6%)
Iris neovascularization	12 (4.6%)	2 (0.8%)	1 (0.4%)
Iritis	7 (2.7%)	3 (1.1%)	2 (0.8%)
Keratitis	0	1 (0.4%)	3 (1.2%)
Lacrimation increased	7 (2.7%)	10 (3.8%)	5 (1.9%)
Macular edema	16 (6.2%)	9 (3.4%)	5 (1.9%)
Macular ischemia	3 (1.2%)	0	0
Maculopathy	19 (7.3%)	36 (13.5%)	28 (10.8%)
Metamorphopsia	3 (1.2%)	5 (1.9%)	3 (1.2%)
Ocular discomfort	6 (2.3%)	3 (1.1%)	6 (2.3%)
Ocular hyperemia	7 (2.7%)	18 (6.8%)	13 (5.0%)
Optic atrophy	1 (0.4%)	0	4 (1.5%)

MedDRA System Organ Class Preferred Term	Sham N=260	Ranibizumab Pooled	
		0.3 mg N=266	0.5 mg N=259
Optic disc vascular disorder	8 (3.1%)	13 (4.9%)	2 (0.8%)
Ocular vascular disorder	13 (5.0%)	17 (6.4%)	17 (6.6%)
Papilledema	5 (1.9%)	3 (1.1%)	2 (0.8%)
Photopsia	3 (1.2%)	4 (1.5%)	4 (1.5%)
Punctate keratitis	2 (0.8%)	5 (1.9%)	4 (1.5%)
Retinal depigmentation	11 (4.2%)	17 (6.4%)	23 (8.9%)
Retinal disorder	3 (1.2%)	3 (1.1%)	6 (2.3%)
Retinal exudates	33 (12.7%)	69 (25.9%)	54 (20.8%)
Retinal hemorrhage	29 (11.2%)	32 (12.0%)	29 (11.2%)
Retinal neovascularization	8 (3.1%)	2 (0.8%)	2 (0.8%)
Retinal pigmentation	9 (3.5%)	8 (3.0%)	6 (2.3%)
Retinal vascular disorder	24 (9.2%)	30 (11.3%)	32 (12.4%)
Retinal vein occlusion	3 (1.2%)	2 (0.8%)	1 (0.4%)
Vision blurred	8 (3.1%)	9 (3.4%)	12 (4.6%)
Visual acuity reduced	3 (1.2%)	0	3 (1.2%)
Visual impairment	3 (1.2%)	6 (2.3%)	2 (0.8%)
Vitreous detachment	6 (2.3%)	7 (2.6%)	10 (3.9%)
Vitreous floaters (Myodesopsia)	6 (2.3%)	26 (9.8%)	18 (6.9%)
Vitreous hemorrhage	15 (5.8%)	11 (4.5%)	9 (3.5%)
Gastrointestinal Disorders			
Diarrhea	7 (2.7%)	5 (1.9%)	1 (0.4%)
Dyspepsia	4 (1.5%)	0	1 (0.4%)
Gastroesophageal reflux disease	1 (0.4%)	3 (1.1%)	2 (0.8%)
Nausea	4 (1.5%)	2 (0.8%)	3 (1.2%)
Toothache	3 (1.2%)	2 (0.8%)	2 (0.8%)
Vomiting	4 (1.5%)	1 (0.4%)	3 (1.2%)
General Disorders and Administration Site Conditions			
Edema peripheral	3 (1.2%)	2 (0.8%)	1 (0.4%)
Pain	2 (0.8%)	3 (1.1%)	2 (0.8%)
Immune System Disorders			
Hypersensitivity	1 (0.4%)	2 (0.8%)	4 (1.5%)
Seasonal allergy	5 (1.9%)	4 (1.5%)	1 (0.4%)
Infections and Infestations			
Bronchitis	4 (1.5%)	3 (1.1%)	1 (0.4%)
Cystitis	1 (0.4%)	1 (0.4%)	3 (1.2%)
Influenza	5 (1.9%)	4 (1.5%)	8 (3.1%)
Nasopharyngitis	10 (3.8%)	14 (5.3%)	14 (5.4%)
Pneumonia	4 (1.5%)	4 (1.5%)	1 (0.4%)
Sinusitis	5 (1.9%)	14 (5.3%)	8 (3.1%)
Upper respiratory tract infection	4 (1.5%)	7 (2.6%)	6 (2.3%)
Urinary tract infection	4 (1.5%)	5 (1.9%)	2 (0.8%)
Injury, Poisoning and Procedural Complications Contrast Media Reaction			
Contusion	5 (1.9%)	2 (0.8%)	4 (1.5%)
Fall	6 (2.3%)	2 (0.8%)	5 (1.9%)
Upper limb fracture	0	3 (1.1%)	0
Investigations			
Blood pressure increased	2 (0.8%)	2 (0.8%)	3 (1.2%)

MedDRA System Organ Class Preferred Term	Sham N=260	Ranibizumab Pooled	
		0.3 mg N=266	0.5 mg N=259
Metabolism and Nutrition Disorders			
Hypercholoesterolemia	3 (1.2%)	4 (1.5%)	2 (0.8%)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	2 (0.8%)	3 (1.1%)	6 (2.3%)
Arthritis	1 (0.4%)	3 (1.1%)	2 (0.8%)
Back pain	2 (0.8%)	4 (1.5%)	7 (2.7%)
Muscle spasms	4 (1.5%)	0	2 (0.8%)
Neck pain	1 (0.4%)	3 (1.1%)	0
Osteoarthritis	1 (0.4%)	4 (1.5%)	0
Osteoporosis	1 (0.4%)	0	3 (1.2%)
Pain in extremity	2 (0.8%)	3 (1.1%)	2 (0.8%)
Nervous System Disorders			
Dizziness	9 (3.5%)	6 (2.3%)	2 (0.8%)
Headache	9 (3.5%)	13 (4.9%)	7 (2.7%)
Sinus headache	1 (0.4%)	0	3 (1.2%)
Psychiatric Disorders			
Anxiety	4 (1.5%)	4 (1.5%)	2 (0.8%)
Depression	1 (0.4%)	2 (0.8%)	3 (1.2%)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	4 (1.5%)	3 (1.1%)	4 (1.5%)
Nasal congestion	4 (1.5%)	1 (0.4%)	0
Sinus congestion	1 (0.4%)	2 (0.8%)	4 (1.5%)
Skin and Subcutaneous Disorders			
Hyperhidrosis	0	0	3 (1.2%)
Rash	3 (1.2%)	2 (0.8%)	2 (0.8%)
Vascular Disorders			
Hypertension	21 (8.1%)	16 (6.0%)	13 (5.0%)

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

Reviewer's Comment:

Ocular adverse events which occurred most frequently (i.e. > 2%) in the study eye of the ranibizumab treatment groups were cataract, conjunctival hemorrhage, eye discharge, eye irritation, eye pain, foreign body sensation in eyes, maculopathy, ocular hyperemia, ocular vascular disorder, retinal depigmentation, retinal disorder, retinal exudates, retinal vascular disorder, vitreous detachment.. Many of these adverse events are commonly associated with the condition treated, as well as, conjunctival anesthetic and intravitreal injection procedures.

Non-ocular adverse events which occurred in > 2% of ranibizumab-treated patients compared to control were: nasopharyngitis (5.4% vs. 3.8%), influenza (3.1% vs. 1.9%), back pain (2.7% vs. 0.8%), arthralgia (2.3% vs. 0.8%), sinusitis (3.1% vs. 1.9%) and upper respiratory infection (2.3% vs. 1.5%).

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

Refer to Section 7.1.3.3 which contains tables of the Serious Adverse Events Potentially Related to Systemic VEGF Inhibition, APTC Arterial Thromboembolic Events, and Intraocular Inflammation in the Study Eye during the 6-Month Treatment Period for the Safety Evaluable Subjects in the Pooled population of Studies FVF4165g and FVF4166g for details.

7.1.5.6 Additional analyses and explorations

Refer to Section 7.4.1.1.

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 the 6-month treatment period, laboratory samples were obtained at screening (baseline) and at the early termination visit for subjects who discontinued from the study early. No clinically relevant changes from baseline in laboratory results were noted for subjects who discontinued from the study early.

Refer to Section 7.1.10 for details.

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

No additional assessments were performed.

7.1.8 Vital Signs

Vital signs were taken at screening and prior to dosing at each monthly visit. Overall, results between treatment groups were similar, with both ranibizumab- and sham-treated subjects showing little mean change from baseline in vital signs throughout the 6-month treatment period.

The changes from baseline in blood pressure, on average, were within a narrow range of between −4.2 and −0.4 mmHg over time for all three treatment groups. At Month 6, the mean changes from baseline were −0.4, −4.2, and −1.3 mmHg in systolic pressure and −1.0, −1.8, and −0.5 mmHg in diastolic pressure for the sham, 0.3-mg, and 0.5-mg groups, respectively. In addition, there was no imbalance in the incidence of hypertension (> 150/100 mmHg) or severe hypertension (> 200/110 mmHg) between the treatment groups.

Table 7.1.8-1 Incidence of Hypertension or Severe Hypertension during the 6-Month Treatment Period Studies FVF4165g and FVF4166g Pooled

	Sham (n=260)	Ranibizumab	
		0.3 mg (n=266)	0.5 mg (n=259)
Number of subjects with any post-baseline assessment	258	264	256
Hypertension (>150/100 mmHg)	92 (35.7%)	101 (38.3%)	92 (35.9%)
Severe hypertension (>200/110 mmHg)	3 (1.2%)	3 (1.1%)	2 (0.8%)

Note: Subjects were considered to have hypertension or severe hypertension if they had either a systolic or diastolic reading greater than the cutoff value on one or more occasions post-baseline. On days of injection, blood pressure was measured prior to injection.

7.1.8.1 Overview of vital signs testing in the development program

Refer to Section 7.1.8.

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 were not performed.

7.1.9 Electrocardiograms (ECGs)

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

7.1.10 Immunogenicity

During the 6-month treatment period, serum samples for the evaluation of antibodies to ranibizumab were obtained at screening (baseline) and at Month 6, prior to study drug administration. Of the subjects with evaluable samples at baseline, 3.5%, 2.7%, and 3.2% of subjects in the sham, 0.3-mg, and 0.5-mg groups, respectively, tested positive for antibodies to ranibizumab, possibly due to preexisting anti-Fab antibodies1. At Month 6, 3.6%, 1.7%, and 2.7% of subjects with evaluable samples in the sham, 0.3-mg, and 0.5-mg groups, respectively, tested positive for antibodies to ranibizumab.

Adverse events and visual acuity outcomes for subjects who tested positive for antibodies to ranibizumab at any timepoint during the 6-month treatment period were reviewed. Changes in visual acuity from baseline to Month 6 were consistent with the larger study population. When subjects with and without positive antibody responses were compared, no clinically significant differences in adverse events were found.

Table 7.1.10-1 Antibodies to Ranibizumab during the 6-Month Treatment Period Safety Evaluable Subjects

Timepoint	No. of Subjects Who Tested Positive for Antibodies / No. of Subjects with Evaluable Samples (%)		
	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Baseline	6/129 (4.7%)	1/129 (0.8%)	5/127 (3.9%)
Month 6	4/112 [a] (3.6%)	2/117 (1.7%)	3/112 [b] (2.7%)

Note: The baseline sample was taken at the screening visit
a In the sham group, 2 subjects who tested positive for antibodies to ranibizumab at baseline were not re-tested at Month 6.
b In the 0.5 mg group, 3 subjects who tested positive for antibodies to ranibizumab at baseline were not re-tested at Month 6.

Table 7.1.10-2 Antibodies to Ranibizumab at Month 6 by Baseline Antibody Status Safety Evaluable Subjects

1 Süsal C, Döhler B, Opelz G. Graft-protective role of high pretransplantation IgA-anti-Fab autoantibodies: confirmatory evidence obtained in more than 4000 kidney transplants. The Collaborative Transplant Study. Transplantation. 2000 Apr 15;69(7):1337-40

Timepoint	No. of Subjects Who Tested Positive for Antibodies at Month 6 / No. of Subjects with Specified Baseline Status Who Were Tested at Month 6		
	Sham	Ranibizumab	
		0.3 mg	0.5 mg
Positive	4/4 [a]	1/1	2/2 [b]
Negative	0/107	1/112	1/110
Missing	0/1	0/4	0/0

Note: The baseline sample was taken at the screening visit
a In the sham group, 2 subjects who tested positive for antibodies to ranibizumab at baseline were not re-tested at Month 6.
b In the 0.5 mg group, 3 subjects who tested positive for antibodies to ranibizumab at baseline were not re-tested at Month 6

Reviewer's Comment:
Adverse events and visual acuity outcomes for subjects who tested positive for antibodies to ranibizumab at any timepoint during the 6-month treatment period were reviewed. Changes in visual acuity from baseline to Month 6 were consistent with the larger study population. When subjects with and without positive antibody responses were compared, no clinically significant differences in adverse events were found.

7.1.11 Human Carcinogenicity

No known potential to be carcinogenic.

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 retinal vein occlusions, 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

Lucentis (ranibizumab injection) has been marketed since its approval on June 30, 2006. No postmarketing data or experience has been submitted to the Division which affects the safety or efficacy of the product.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

Refer to Section 4.2.

7.2.1.2 Demographics

7.2.1.2.1 Study FVF4165g

Table 7.2.1.2.1-1 Subject Demographics by Treatment Group Randomized Subjects

Demographic	Sham (n = 132)	Ranibizumab 0.3 mg (n = 134)	Ranibizumab 0.5 mg (n = 131)
Age (yr)			
Mean (SD)	65.2 (12.7)	66.6 (11.2)	67.5 (11.8)
Range	26-89	43-90	41-91
Age group (yr), n (%)			
< 45	8 (6.1%)	5 (3.7%)	4 (3.1%)
45 to < 65	59 (44.7%)	51 (38.1%)	51 (38.9%)
65 to < 85	60 (45.5%)	74 (55.2%)	69 (52.7%)
≥ 85	5 (3.8%)	4 (3.0%)	7 (5.3%)
Sex			
Male	74 (56.1%)	67 (50.0%)	71 (54.2%)
Female	58 (43.9%)	67 (50.0%)	60 (45.8%)
Race/ethnicity			
White	108 (81.8%)	112 (83.6%)	107 (81.7%)
Black	13 (9.8%)	11 (8.2%)	13 (9.9%)
Hispanic or Latino	9 (6.8%)	11 (8.2%)	7 (5.3%)
Asian	6 (4.5%)	1 (0.7%)	5 (3.8%)
American Indian or Alaska Native	2 (1.5%)	2 (1.5%)	0
Not Available	4 (3.0%)	9 (6.7%)	6 (4.6%)

a Multi-racial subjects were counted in each race category that they indicated.

Reviewer's Comment:
The demographics of the subjects in the study were well balanced. The predominance of adults in their 5th through 7th decades of life is representative of the population affected by this disease.

The treatment groups were balanced in terms of baseline demographics.

Table 7.2.1.2.1-2 Baseline Ocular Characteristics in the Study Eye Intent-to-Treat, Randomized Subjects

Characteristics	Sham (n = 132)	Ranibizumab 0.3 mg (n = 134)	Ranibizumab 0.5 mg (n = 131)
Months since diagnosis of RVO			
Mean (SD)	3.7 (3.7)	3.6 (4.1)	3.3 (3.1)
Range	0.0 – 16.0	0.0 – 35.0	0.0 - 13.0
Visual acuity			
Number of letters (0–100)			
Mean (SD)	54.7 (12.2)	56.0 (12.1)	53.0 (12.5)
Range	16-73	25-73	22-79
≤ 34	9 (6.8%)	9 (6.7%)	13 (9.9%)
35-54	50 (37.9%)	48 (35.8%)	49 (37.4%)
≥ 55	73 (55.3%)	77 (57.5%)	69 (52.7%)
Approximate Snellen equivalent			
Median	20/80	20/63-20/80	20/80
20/200 or worse	14 (10.6%)	14 (10.4%)	21 (16.0%)
Better than 20/200 but worse than 20/40	99 (75.0%)	99 (73.9%)	95 (72.5%)
20/40 or better	19 (14.4%)	21 (15.7%)	15 (11.5%)

Reviewer's Comment:
The baseline ocular characteristics of the study eye were well balanced.

The mean number of months since the diagnosis of retinal vein occlusion was between 3 and 4 months.

The mean baseline visual acuity ranged from 53.0 to 56.0 letters (approximate Snellen equivalent 20/80) at a starting test distance of 4 meters. The majority of subjects had baseline visual acuity of ≥ 55 letters.

Table 7.2.1.2.1-3 Baseline Fundus Photography Characteristics in the Study Eye Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Type of vein occlusion, n (%)			
n	130	133	129
Absent	1 (0.8%)	2 (1.5%)	0
Questionable	0	1 (0.8%)	3 (2.3%)
Macular branch only	4 (3.1%)	3 (2.3%)	6 (4.7%)
Branch: ≤ 1 quadrant	91 (70.0%)	87 (65.4%)	80 (62.0%)
Branch: > 1 quadrant	11 (8.5%)	21 (15.8%)	20 (15.5%)
Hemicentral	17 (13.1%)	16 (12.0%)	17 (13.2%)
Central: All 4 quadrants involved	1 (0.8%)	0	1 (0.8%)
Cannot grade	5 (3.8%)	3 (2.3%)	2 (1.6%)
Primary vein occlusion location, n (%)			
n	130	133	129
Superior	69 (53.1%)	66 (49.6%)	76 (58.9%)
Inferior	53 (40.8%)	61 (45.9%)	46 (35.7%)
Indeterminate	0	0	1 (0.8%)
Cannot grade	1 (0.8%)	0	0
Not applicable	7 (5.4%)	6 (4.5%)	6 (4.7%)
Collateral vessels on disc, n (%)			
n	132	134	131
Absent	87 (65.9%)	91 (67.9%)	84 (64.1%)
Questionable	9 (6.8%)	10 (7.5%)	15 (11.5%)
Definite, < standard 2	22 (16.7%)	17 (12.7%)	21 (16.0%)
Definite, ≥ standard 2	12 (9.1%)	15 (11.2%)	11 (8.4%)
Cannot grade	2 (1.5%)	1 (0.7%)	0
New vessels on disc, n (%)			
n	132	134	131
Absent	128 (97.0%)	133(99.3%)	130 (99.2%)
Questionable	2 (1.5%)	0	1 (0.8%)
Definite, < 1/4 DA	0	0	0
Definite, ≥ 1/4 DA	1 (0.8%)	0	0
Cannot grade	1 (0.8%)	1 (0.7%)	0
Total area of retinal hemorrhage, center subfield, calculated (DA)			
n	129	132	131
Mean (SD)	0.121 (0.137)	0.103 (0.129)	0.117 (0.131)
Median	0.05	0.04	0.05
Range	0.00-0.44	0.00-0.44	0.00-0.44

Reviewer's Comment:
The baseline ocular characteristics of the study eye by fundus photography were well balanced.

The majority of subjects had less than or equal to one branch of a retinal vessel involved. Twelve to thirteen percent had hemiretinal vein occlusions. Two subjects had all 4 quadrants involved.

There was a slight preponderance of superior retinal involvement. Sixty four to sixty eight percent of subjects did not have collateral vessels on disc.

New vessels on the disc were absent in 97-99% of subjects.

Table 7.2.1.2.1-4 Baseline Fluorescein Angiography Characteristics of the Study Eye Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Total area of capillary loss in center, inner, and outer subfields, calculated (DA)			
n	124	125	118
Mean (SD)	1.028 (1.859)	0.757 (1.549)	1.028 (2.053)
Median	0.00	0.00	0.00
Range	0.00-7.98	0.00-6.97	0.00-9.03
Total area of fluorescein leakage in center, inner, and outer subfields, calculated (DA)			
n	131	133	130
Mean (SD)	6.387 (2.505)	6.495 (2.627)	6.589 (2.867)
Median	6.70	6.33	6.56
Range	0.13-11.79	1.24-13.45	0.67-16.00
Total area of cystoid changes in center, inner, and outer subfields, calculated (DA)			
n	131	133	130
Mean (SD)	0.299 (0.686)	0.385 (0.831)	0.256 (0.697)
Median	0.00	0.00	0.00
Range	0.00-4.59	0.00-5.77	0.00-4.80

DA = disc area

Reviewer's Comment:
There was no significant difference in the baseline characteristics of the fluorescein angiography of the study eye across the treatment groups.

Table 7.2.1.2.1-5 Baseline Optical Coherence Tomography Characteristics in the Study Eye Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Central foveal thickness (µm) [a]			
n	132	134	131
Mean (SD)	488.0 (192.2)	522.1 (201.9)	551.7 (223.5)
Median	480.5	499.0	502.0
Range	117-1040	154-1170	197-1485
Distribution, n (%)			
< 450 µm	61 (46.2%)	53 (39.6%)	48 (36.6%)
≤ 450 µm	71 (53.8%)	81 (60.4%)	83 (63.4%)
Central subfield thickness (µm)			
n	98	115	105
Mean (SD)	483.2 (134.4)	488.0 (142.9)	491.3 (139.2)
Median	461.5	465.0	473.0
Range	211-836	272-943	239-878
Distribution, n (%)			
< 450 µm	45 (45.9%)	53 (46.1%)	44 (41.9%)
≤ 450 µm	53 (54.1%)	62 (53.9%)	61 (58.1%)
Total macular volume (mm^3)			
n	131	133	130
Mean (SD)	9.641 (1.831)	9.640 (1.833)	9.839 (2.151)
Median	9.35	9.18	9.50
Range	6.56-14.99	6.53-16.12	6.91-16.98

a Central foveal thickness was defined as the center point thickness

Reviewer's Comment:

The mean central subfield thickness was similar between groups at baseline. The mean central foveal thickness of study eye was lower in the sham group (488 µm) compared with the ranibizumab groups (522 µm and 552 µm for the 0.3 mg and 0.5 mg groups, respectively).

Mean total macular volume was similar across the three treatment groups.

Table 7.2.1.2.1-6 Targeted Medical History: Events Occurring in 2 or More Subjects Randomized Subjects

Diagnosis	Sham (n=132)	Ranibizumab 0.3 mg (n=134)	Ranibizumab 0.5 mg (n=131)
Open angle glaucoma	10 (7.6%)	18 (13.4%)	18 (13.7%)
Hypertension	91 (68.9%)	101 (75.4%)	92 (70.2%)
Angina	12 (9.1%)	7 (5.2%)	9 (6.9%)
Myocardial infarction	12 (9.1%)	8 (6.0%)	9 (6.9%)
Congestive heart failure	6 (4.5%)	6 (4.5%)	3 (2.3%)
Transient ischemic attack	7 (5.3%)	5 (3.7%)	7 (5.3%)
CVA – ischemic	5 (3.8%)	5 (3.7%)	3 (2.3%)
CVA – hemorrhagic	0	0	3 (2.3%)
Prior non-ocular hemorrhage	2 (1.5%)	1 (0.7%)	2 (1.5%)
Deep vein thrombosis	0	2 (1.5%)	5 (3.8%)
Endarterectomy	1 (0.8%)	2 (1.5%)	1 (0.8%)
Diabetes mellitus	27 (20.5%)	20 (14.9%)	25 (19.1%)
Lymphoma	2 (1.5%)	1 (0.7%)	0

Reviewer's Comment:
The majority of patients in Study FVF4165g had hypertension. A significant percentage also had diabetes mellitus, coronary artery disease (i.e., angina and myocardial infarction) and open angle glaucoma. All of these conditions are associated with vein occlusion.

Table 7.2.1.2.1-7 Prior Therapies for Retinal Vein Occlusion in the Study Eye Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Any prior therapy for RVO	25 (18.9%)	25 (18.7%)	21 (16.0%)
Anti-VEGF treatment	8 (6.1%)	10 (7.5%)	7 (5.3%)
Triamcinolone	10 (7.6%)	5 (3.7%)	10 (7.6%)
Other [a]	17 (12.9%)	14 (10.4%)	13 (9.9%)

a All therapies identified as "other" involved laser therapy.

Reviewer's Comment:
Approximately 16-19% of subjects had prior therapy for retinal vein occlusion in the study eye.

Table 7.2.1.2.1-8 Concurrent Ocular Procedures in the Study Eye during the 6-Month Treatment Period (Randomized Subjects)

Disease Category / Ocular Procedure [a]	Sham (n=132)	Ranibizumab 0.3 mg (n=134)	Ranibizumab 0.5 mg (n=131)
All disease categories			
Any ocular procedure	3 (2.3%)	2 (1.5%)	1 (0.8%)
Cataract (including post-cataract surgery)			
Any ocular procedure	1 (0.8%)	1 (0.7%)	0
YAG capsulotomy	0	1 (0.7%)	0
YAG laser capsulotomy	1 (0.8%)	0	0
Vitreoretinal disease (non-AMD)			
Any ocular procedure	0	1 (0.7%)	0
Cryotherapy	0	1 (0.7%)	0
Pneumatic retinopexy	0	1 (0.7%)	0
Other disease			
Any ocular procedure	2 (1.5%)	0	1 (0.8%)
(PRP) panretinal photocoagulation	1 (0.8%)	0	0
Pan retinal photocoagulation	1 (0.8%)	0	0
Pars plana lensectomy	0	0	1 (0.8%)
Pars plana vitrectomy	0	0	1 (0.8%)
Vitreous tap	0	0	1 (0.8%)

a Central foveal thickness was defined as the center point thickness

Reviewer's Comment:

The number of concurrent ocular procedures was higher in the sham group. Ocular procedures performed during the 6 month treatment period were laser procedures.

7.2.1.2.2 Study FVF4166g

Table 7.2.1.2.2-1 Subject Demographics by Treatment Group Randomized Subjects

Demographic	Sham (n = 130)	Ranibizumab 0.3 mg (n = 132)	Ranibizumab 0.5 mg (n = 130)
Age (yr)			
Mean (SD)	65.4 (13.1)	69.7 (11.6)	67.6 (12.4)
Range	20-91	38-90	40-91
Age group (yr), n (%)			
< 45	10 (7.7%)	5 (3.8%)	5 (3.8%)
45 to < 65	50 (38.5%)	36 (27.3%)	46 (35.4%)
65 to < 85	67 (51.5%)	80 (60.62%)	71 (54.6%)
≥ 85	3 (2.3%)	11 (8.3%)	8 (6.2%)
Sex			
Male	72 (55.4%)	71 (53.8%)	80 (61.5%)
Female	58 (44.6%)	61 (46.2%)	50 (38.5%)
Race/ethnicity			
White	113 (86.9%)	108 (81.8%)	108 (83.1%)
Black	8 (6.2%)	16 (12.1%)	10 (7.7%)
Hispanic or Latino	15 (11.5%)	16 (12.1%)	10 (7.7%)
Asian	6 (4.6%)	3 (2.3%)	6 (4.6%)
American Indian or Alaska Native	1 (0.8%)	0	1 (0.8%)
Native Hawaiian or Pacific Islander	0	0	2 (1.5%)
Not Available	3 (2.3%)	5 (3.8%)	5 (3.8%)

a Multi-racial subjects were counted in each race category that they indicated.

Reviewer's Comment:
The demographics of the subjects in the study were well balanced. The predominance of adults in their 5th through 7th decades of life is representative of the population affected by this disease.

The treatment groups were relatively balanced regarding the subjects' baseline demographics.

Table 7.2.1.2.2-2 Baseline Ocular Characteristics in the Study Eye Intent-to-Treat, Randomized Subjects

Characteristics	Sham (n = 132)	Ranibizumab 0.3 mg (n = 134)	Ranibizumab 0.5 mg (n = 131)
Months since diagnosis of RVO			
Mean (SD)	2.9 (2.9)	3.6 (3.2)	3.3 (3.7)
Range	0.0 – 14.0	0.0 – 12.0	0.0 - 27.0
Visual acuity			
Number of letters (0–100)			
Mean (SD)	49.2 (14.7)	47.4 (14.8)	48.1 (14.6)
Range	16-71	9-72	21-73
≤ 34	26 (20.0%)	33 (25.0%)	30 (23.1%)
35-54	49 (37.7%)	46 (34.8%)	50 (38.5%)
≥ 55	55 (42.3%)	53 (40.2%)	50 (38.5%)
Approximate Snellen equivalent			
Median	20/100	20/100	20/100
20/200 or worse	35 (26.9%)	41 (31.1%)	39 (30.0%)
Better than 20/200 but worse than 20/40	83 (63.8%)	82 (62.1%)	84 (64.6%)
20/40 or better	12 (9.2%)	9 (6.8%)	7 (5.4%)

Reviewer's Comment:
The baseline ocular characteristics of the study eye were well balanced.

The mean number of months since the diagnosis of retinal vein occlusion was approximately 3 months.

The mean baseline visual acuity ranged from 47 to 49 letters (approximate Snellen equivalent 20/100) at a starting test distance of 4 meters. The majority of subjects had baseline visual acuity of between 20/40 and 20/200.

Table 7.2.1.2.2-3 Baseline Fundus Photography Characteristics in the Study Eye Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Type of vein occlusion, n (%)			
n	125	131	129
Absent	1 (0.8%)	0	0
Questionable	0	1 (0.8%)	0
Macular branch only	0	0	0
Branch: ≤ 1 quadrant	0	1 (0.8%)	0
Branch: > 1 quadrant	0	0	0
Hemi-central	2 (1.6%)	1 (0.8%)	1 (0.8%)
Central: All 4 quadrants involved	116 (92.8%)	120 (91.6%)	125 (96.9%)
Could not grade	6 (4.8%)	8 (6.1%)	3 (2.3%)
Primary vein occlusion location, n (%)			
n	125	131	129
Superior	2 (1.6%)	1 (0.8%)	0
Inferior	0	1 (0.8%)	1 (0.8%)
Indeterminate	0	0	0
Could not grade	0	0	0
Not applicable	123 (98.4%)	129 (98.5%)	128 (99.2%)
Collateral vessels on disc, n (%)			
n	130	132	130
Absent	61 (46.9%)	57 (43.2%)	44 (33.8%)
Questionable	24 (18.5%)	22 (16.7%)	34 (26.2%)
Definite, < standard 2	17 (13.1%)	22 (16.7%)	23 (17.7%)
Definite, ≥ standard 2	25 (19.2%)	23 (17.4%)	24 (18.5%)
Could not grade	3 (2.3%)	8 (6.1%)	5 (3.8%)
New vessels on disc, n (%)			
n	130	132	130
Absent	127 (97.7%)	127(96.2%)	126 (96.9%)
Questionable	0	0	1 (0.8%)
Definite, < 1/4 DA	1 (0.8%)	0	1 (0.8%)
Definite, ≥ 1/4 DA	0	0	0
Could not grade	2 (1.5%)	5 (3.8%)	2 (1.5%)
Total area of retinal hemorrhage, center subfield, calculated (DA)			
n	128	125	126
Mean (SD)	0.080 (0.113)	0.093 (0.117)	0.093 (0.117)
Median	0.03	0.04	0.04
Range	0.00-0.44	0.00-0.44	0.00-0.44

Reviewer's Comment:
The baseline ocular characteristics of the study eye by fundus photography were well balanced.

Ninety-two to ninety-seven percent of the patients had a central vein occlusion with all four quadrants involved. Less than 2 percent of patients had a hemi-central vein occlusion.

Disc collateral vessels were present in 32% to 36% of patients. New vessels on the disc were absent in 96-98% of subjects.

Table 7.2.1.2.2-4
Baseline Fluorescein Angiography Characteristics of the Study Eye Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Total area of capillary loss in center, inner, and outer subfields, calculated (DA)			
n	112	113	109
Mean (SD)	0.265 (1.089)	0.166 (0.564)	0.551 (1.951)
Median	0.00	0.00	0.00
Range	0.00-7.59	0.00-4.65	0.00-13.22
Total area of fluorescein leakage in center, inner, and outer subfields, calculated (DA)			
n	128	130	129
Mean (SD)	12.192 (4.602)	11.915 (4.846)	11.911 (4.666)
Median	14.50	14.58	13.88
Range	0.00-16.00	0.00-16.00	0.00-16.00
Total area of cystoid changes in center, inner, and outer subfields, calculated (DA)			
n	128	130	129
Mean (SD)	1.273 (1.753)	1.187 (1.803)	1.151 (1.397)
Median	0.75	0.62	0.68
Range	0.00-12.87	0.00-5.77	0.00-6.15

DA = disc area

Reviewer's Comment:
There were no significant differences in the baseline characteristics of the fluorescein angiography of the study eye across the treatment groups.

Table 7.2.1.2.2-5
Baseline Optical Coherence Tomography Characteristics in the Study Eye
Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Central foveal thickness (µm) [a]			
n	129	131	130
Mean (SD)	687.0 (237.6)	679.9 (242.4)	688.7 (253.1)
Median	684.0	673.0	672.0
Range	203-1338	174-1527	126-1651
Distribution, n (%)			
< 450 µm	20 (15.5%)	23 (17.6%)	19 (14.6%)
≤ 450 µm	109 (84.5%)	108 (82.4%)	111 (85.4%)
Central subfield thickness (µm)			
n	97	104	91
Mean (SD)	595.2 (149.0)	585.8 (169.4)	602.8 (152.2)
Median	599.0	594.5	599.0
Range	310-949	252-1045	253-934
Distribution, n (%)			
< 450 µm	17 (17.5%)	24 (23.1%)	15 (16.5%)
≤ 450 µm	80 (82.5%)	80 (76.9%)	76 (83.5%)
Total macular volume (mm^3)			
n	86	93	74
Mean (SD)	10.700 (2.303)	10.748 (2.380)	10.308 (2.033)
Median	10.17	10.67	9.98
Range	6.45-16.03	7.13-16.50	6.94-16.06

a Central foveal thickness was defined as the center point thickness

Reviewer's Comment:

The mean central foveal thickness was similar between groups at baseline. The mean central subfield thickness of study eye was lowest in the 0.3 mg group (585.8 µm) compared with the sham (595.2 µm) and 0.5 mg (602.8 µm) groups, respectively.

Mean total macular volume was similar across the three treatment groups.

Table 7.2.1.2.2-6
Targeted Medical History: Events Occurring in 2 or More Subjects
Randomized Subjects

Diagnosis	Sham (n=130)	Ranibizumab 0.3 mg (n=132)	Ranibizumab 0.5 mg (n=130)
Open angle glaucoma	19 (14.6%)	14 (10.6%)	21 (16.2%)
Hypertension	88 (67.7%)	96 (72.7%)	90 (69.2%)
Angina	8 (6.2%)	4 (3.0%)	13 (10.0%)
Myocardial infarction	8 (6.2%)	7 (5.3%)	10 (7.7%)
Congestive heart failure	4 (3.1%)	5 (3.8%)	2 (1.5%)
Transient ischemic attack	3 (2.3%)	5 (3.8%)	3 (2.3%)
CVA, ischemic	4 (3.1%)	6 (4.5%)	2 (1.5%)
Prior non-ocular hemorrhage	0	3 (2.3%)	3 (2.3%)
Deep vein thrombosis	0	2 (1.5%)	1 (0.8%)
Endarterectomy	0	1 (0.8%)	3 (2.3%)
Diabetes Mellitus	28 (21.5%)	31 (23.5%)	30 (23.1%)
Sarcoidosis	0	2 (1.5%)	1 (0.8%)
Lyme disease	1 (0.8%)	1 (0.8%)	1 (0.8%)
Leukemia	0	1 (0.8%)	1 (0.8%)

Note: No subjects in any treatment group had a history of a hemorrhagic cerebrovascular accident.

Reviewer's Comment:
As in Study FVF4165g, the majority of patients were hypertensive. Many patients also had diabetes mellitus, coronary artery disease (i.e., angina, myocardial infarction) and open angle glaucoma.

Table 7.2.1.2.2-7 Prior Therapies for Retinal Vein Occlusion in the Study Eye
Randomized Subjects

Characteristics	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Any prior therapy for RVO	17 (13.1%)	20 (15.2%)	16 (12.3%)
Anti-VEGF treatment	9 (6.9%)	11 (8.3%)	8 (6.2%)
Triamcinolone	5 (3.8%)	7 (5.3%)	7 (5.4%)
Medication, other	2 (1.5%)	2 (1.5%)	1 (0.8%)
Other [a]	3 (2.3%)	7 (5.3%)	4 (3.1%)

a All therapies identified as "other" involved laser therapy.

Reviewer's Comment:
Approximately 16-20% of subjects had prior therapy for retinal vein occlusion in the study eye.

Table 7.2.1.2.2-8
Concurrent Ocular Procedures in the Study Eye during the 6-Month Treatment Period
Randomized Subjects

Disease Category and Ocular Procedure [a]	Sham (n=130)	Ranibizumab 0.3 mg (n=132)	Ranibizumab 0.5 mg (n=130)
All disease categories			
Any ocular procedure	8 (6.2%)	5 (3.8%)	2 (1.5%)
Cataract (including post-cataract surgery)			
Any ocular procedure	0	2 (1.5%)	1 (0.8%)
Cataract extraction with IOL implant	0	1 (0.8%)	0
Cataract surgery	0	1 (0.8%)	0
Phaco cataract extraction with IOL implant	0	0	1 (0.8%)
Iris Neovascularization			
Any ocular procedure	4 (3.1%)	1 (0.8%)	0
Pan retinal photocoagulation laser	1 (0.8%)	0	0
Pan retinal photocoagulation OS	1 (0.8%)	0	0
Pan retinal photocoagulation	0	1 (0.8%)	0
PRP	1 (0.8%)	0	0
PRP laser	1 (0.8%)	0	0
Neovascular glaucoma			
Any ocular procedure	1 (0.8%)	0	0
Pan retinal photocoagulation	1 (0.8%)	0	0
Other glaucoma			
Any ocular procedure	0	1 (0.8%)	0
Paracentesis	0	1 (0.8%)	0
Other			
Any ocular procedure	4 (3.1%)	1 (0.8%)	1 (0.8%)
Avastin injection	1 (0.8%)	0	0
Blepharoplasty	0	0	1 (0.8%)
Pan retinal photocoagulation laser	1 (0.8%)	0	0
Paracentesis	0	1 (0.8%)	0
Scatter photocoagulation (PRP)	1 (0.8%)	0	0
Surgical removal of metallic foreign body	1 (0.8%)	0	0

Note: Individual procedure counts may not sum to class totals because of multiple procedure per subject.
a Ocular procedure terms are as reported by investigators.

Reviewer's Comment:

As in Study FVF4165g, patients in Study FVF4166g had more concurrent ocular procedures in the sham group. These procedures were almost exclusively laser procedures.

7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3-1
Extent of Study Drug Exposure during the 6-Month Treatment Period: Studies FVF4165g and FVF4166g Pooled

	Sham (n=260)	Ranibizumab 0.3 mg (n=266)	Ranibizumab 0.5 mg (n=259)
Number of Injections [a]			
Total	1436	1534	1465
Mean (SD) [b]	5.5 (1.1)	5.8 (0.8)	5.7 (1.0)
Frequency [b]			
1	8 (3.1%)	4 (1.5%)	8 (3.1%)
2	5 (1.9%)	2 (0.8%)	1 (0.4%)
3	7 (2.7%)	1 (0.4%)	2 (0.8%)
4	6 (2.3%)	3 (1.1%)	3 (1.2%)
5	31 (11.9%0	25 (9.4%)	33 (12.7%)
6	203 (78.1%)	231 (86.8%)	212 (81.9%)
Treatment duration (days) [c]			
Mean (SD)	141.4 (34.0)	147.9 (22.4)	145.8 (28.5)
Range	1-171	1-176	1-174

Reviewer's Comment:
The extent of exposure was very similar in each study. Presentation of the pooled exposure is an accurate representation of the findings in either study alone.

In Study FVF4165g, the mean number of injections was 5.6 – 5.7. Seventy-seven to eighty-six percent of subjects received six injections. In Study FVF4166g, the mean number of injections was 5.5-5.8. Seventy nine to eighty-eight percent of subjects received six injections.

Table 7.2.1.3-2
Treatment Held per Protocol-Specified Criteria during the 6-Month Treatment Period: Studies FVF4165g and FVF4166g Pooled

Criterion	Sham (n=260)	Ranibizumab 0.3 mg (n=266)	Ranibizumab 0.5 mg (n=259)
Any treatment held	2 (0.8%)	3 (1.1%)	1 (0.4%)
Visual acuity loss	1 (0.4%)	1 (0.4%)	0
Intraocular pressure	1 (0.4%)	0	0
Sensory rhegmatogenous retinal break or detachment	0	1 (0.4%)	0
Intraocular surgery	1 (0.4%0	1 (0.4%)	1 (0.4%)

a All therapies identified as "other" involved laser therapy.

Reviewer's Comment:
Approximately 16-20% of subjects had prior therapy for retinal vein occlusion in the study eye.

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 literature.

7.2.2.1 Other studies

No other studies were used to evaluate safety.

7.2.2.2 Postmarketing experience

No postmarketing data were used in the review of the supplemental BLA.

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 Phase 3 studies, FVF4165g and FVF4166g, 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 safety and efficacy issues during the development program. The study designs were appropriate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No pharmacology toxicology information was submitted in the supplemental BLA.

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

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.

Refer to Sections 7.1.3.3 and 7.4.1.1 for further details.

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 Update to the Integrated Summary of Safety (ISS) was submitted by the applicant on April 14, 2010. The ISS submitted with the original supplemental BLA included data from the 6-month treatment period from the two trials (FVF4165g and FVF4166g). The ISS did not include data from the 6-month observation period of these studies. However, information regarding serious adverse events that occurred during the 6-month observation period by September 15, 2009 was entered into the clinical database as of October 27, 2009 and was submitted as subject narratives in the ISS.

One additional Genentech-sponsored clinical study of ranibizumab in RVO was ongoing at the time of the sBLA submission and remains ongoing. Study FVF3426g is an uncontrolled, open-label extension study that includes a cohort of subjects with RVO (Cohort 2) who completed Study FVF4165g or FVF4166g. Data from this study were not included in the ISS. However, information regarding serious adverse events that occurred in the RVO cohort by 15 September 2009 and were entered into the clinical database as of 27 October 2009 was provided in the form of subject narratives in the ISS.

This update to the ISS included additional safety information available from Studies FVF4165g, FVF4166g, and FVF3426g. For Studies FVF4165g and FVF4166g, this ISS update includes:

- Additional narratives for subjects with serious adverse events that occurred during the 6-month observation period that were not included in the original ISS; namely, serious adverse events that occurred by 15 September 2009 but were entered into the clinical database after 27 October 2009 or that occurred after 15 September 2009.
- For Study FVF3426g, this ISS update includes additional narratives for subjects in the RVO cohort with serious adverse events that occurred by 14 January 2010 and were entered into the clinical database by 22 February 2010 that were not included in the original ISS. Specifically, this includes serious adverse events that occurred by 15 September 2009 but were entered into the clinical database from 28 October 2009 to 22 February 2010 or that occurred from 16 September 2009 to 14 January 2010 and were entered in to the clinical database by 22 February 2010.

No additional safety analyses are provided in this ISS update for Studies FVF4165g and FVF4166g because the summarization of the final study data, including the 6-month observation period results, is ongoing. In addition, no additional safety analyses are provided for Study FVF3426g because the trial remains ongoing.

Table 7.2.9-1 Subjects Who Experienced Serious Adverse Events during the 6-Month Observation Period – Study FVF4165g

Subject ID	Adverse Event	Day of Onset	Action Taken
	Sham Group		
13703	Serious severe ruptured hemorrhagic bleb in the left upper lobe	188+	Mechanical pleurodesis, LUL wedge resection
0.3 mg Group			
None			
0.5 mg Group			
18303	Cardiac congestive heart failure, bradycardia, chest pain	180+	Hospitalization, meds, AICD implanted
21302	Worsening cataract in fellow eye	186+	None

Reviewer's Comment:
The serious adverse event report for Subject 13703 was reported in the original submission but is updated in this Safety Update.

Table 7.2.9-2 Subjects Who Experienced Serious Adverse Events during the 6-Month Observation Period – Study FVF4166g

Subject ID	Adverse Event	Day of Onset	Action Taken
	Sham Group		
32902	Worsening vitreous hemorrhage > 30 letter loss of VA	210+	None
	0.3 mg Group		
31710	Asthenia (transient weakness)	178+	MRI, Carotid Doppler negative
37505	Macular ischemia > 30 letter loss of VA	300+	
	0.5 mg Group		
31708	Macular edema in the study eye	183+	None
41201	Acute bronchitis	330+	Hospitalized

Reviewer's Comment:
The serious adverse event reports for the 6-month observation period for Study FVF4166g are new reports.

Table 7.2.9-3 Subjects Who Experienced Serious Adverse Events during Study FVF3426g (Cohort 2)

Subject ID	Adverse Event	Action Taken
	Sham Group [a]	
13404	Accidental Fall – Bilateral humerus fractures	Surgery
14602	Worsening Vitreous hemorrhage	Vitrectomy / laser
16501	Exacerbation of cardiac failure	Hospitalization
33204	Pneumonia and Stage IV lung cancer, Death [b]	None
33301	Worsening coronary artery disease	Cardiac cath/ stent placement
33501	Prostate cancer and parotitis	Hospitalization/ meds
35602	Sinus arrhythmia	Pacemaker
35702	Worsening visual acuity	None
35902	Spinal compression fracture	Corticosteroids, back surgery
	0.3 mg Group [a]	
11506	Pancreatic cancer, Death	Unknown
13709	Amaurosis Fugax	None
31301	Acute hypoxic respiratory failure	Meds/ Hospitalization
32104	Non-cardiac chest pain	Hospitalization
33903	Femur fracture, pulmonary embolism, transient ischemic attach and atrial fibrillation	Hospitalization, surgery, medications

Subject ID	Adverse Event	Action Taken
34606	Worsening of cataract	None
0.5 mg Group [a]		
10304	IOP increased (43 mmHg) Iris neovascularization	D/C study. Bevacizumab injection
10703	Massive tear of Left rotator cuff	Surgery
12604	Ischemic optic neuropathy Loss of > 30 letters VA	None
15704	Worsening diplopia	Strabismus surgery
15705	Stroke	None
30401	Intervertebral disc protrusion	Meds/ surgery
30902	Severe CAD – angina at rest	Medication/ angioplasty
33503	Cellulitis of right leg	Antibiotics/ hospitalization
33902	Gram negative septicemia	Antibiotics/ hospitalization
31401	Aortic stenosis	Surgery, medications
34503	Electrolyte imbalance, Loss of > 30 letters VA (secondary to CME)	Laser PRP
10222	Worsening BRVO x 2 [c]	None
31004	Adenocarcinoma and macular edema in study eye	Surgical procedure

a Refers to the treatment group randomization in Study FVF4165g or FVF4166g.
Treatment in Study FVF3426g was 0.5 mg ranibizumab PRN.
b Pneumonia was reported as an AE in Study FVF4166g
c Sinle event of worsening BRVO reported in Study FVF4165g.

Reviewer's Comment:
The serious adverse event reports are consistent with the overall safety database.

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

The dose dependent relationship to intraocular inflammation adverse events observed in the Phase 3 AMD studies of ranibizumab was not seen in Study FVF4165g or Study FVF4166g. Intraocular inflammation was not observed in patients with immunoreactivity in this safety population.

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

The significant adverse event information for the pooled safety population is presented here.

Table 7.4.1.1-1 Adverse Events Potentially Related to Systemic VEGF Inhibition during the 6-Month Treatment Period: Studies FVF4165g and FVF4166g Pooled

MedDRA Preferred Term	Sham (n=260)	Ranibizumab 0.3 mg (n=266)	Ranibizumab 0.5 mg (n=259)
Any adverse event	**32 (12.3%)**	**24 (9.0%)**	**24 (9.3%)**
Arterial thromboembolic events	3 (1.2%)	3 (1.1%)	7 (2.7%)
Hypertension	25 (9.6%)	18 (6.8%)	16 (6.2%)
Non-ocular hemorrhage	6 (2.3%)	5 (1.9%)	3 (1.2%)
Proteinuria	2 (0.8%)	0	0
Other potentially associated events	0	0	1 (0.4%)

Note: Table entries are number (%) of subjects with at least one adverse event of the type specified.

Table 7.4.1.1-2 Myocardial Infarctions, Cerebrovascular Accidents, and Deaths during the 6-Month Treatment Period: Studies FVF4165g and FVF4166g Pooled

Event Type	Sham (n=260)	Ranibizumab 0.3 mg (n=266)	Ranibizumab 0.5 mg (n=259)
Any adverse event	**2 (0.8%)**	**1 (0.4%)**	**3 (1.2%)**
Myocardial infarction	1 (0.4%) [a]	1 (0.4%)	2 (0.8%)
Cerebrovascular accident	1 (0.4%)	0	1 (0.4%)
Vascular death	0	0	1 (0.4%)
APTC arterial thromboembolic event (vascular death, unknown cause death, non-fatal myocardial infarction, non-fatal cerebrovascular accident)	2 (0.8%)	1 (0.4%)	3 (1.2%)

Note: Table entries are number (%) of subjects with at least one adverse event of the type specified.
a Reported as acute coronary syndrome
b Fatal event

7.4.1.2 Combining data

Pooled safety data are presented throughout the safety portion of this review (i.e., Sections 7.1.2, 7.1.3.2, 7.1.5). Studies FVF4165g and FVF4166g 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 applicant 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 for the proposed indication. The frequency of dosing needed is not well established. Dosing every 2 months should be evaluated.

8.2 Drug-Drug Interactions

No important drug-drug interactions have been identified.

8.3 Special Populations

The applicant 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.

8.4 Pediatrics

The applicant requested and received a waiver of the pediatric study requirements for the original Biologics License Application. The waiver was requested because the disease under study macular edema following retinal vein occlusion does not occur in the pediatric age group.

8.5 Advisory Committee Meeting

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

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 was submitted.

8.8 Other Relevant Materials

The comments from the Study Endpoints and Labeling Development review team have been incorporated into this review as appropriate. Please refer to section 6.1.2 for further details.

9 OVERALL ASSESSMENT

9.1 Conclusions

The 6-Month Clinical Study Reports submitted within this Supplemental BLA 125156 for Study FVF4165g, " A Phase 3, Multicenter, Randomized, Sham Injection Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Branch Retinal Vein Occlusion" and Study FVF4166g, "A Phase 3, Multicenter, Randomized, Sham Injection Controlled Study of the Efficacy and Safety of Ranibizumab Injection Compared with Sham in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion" confirms the safety and efficacy for the use of ranibizumab 0.5 mg injection in the treatment of the macular edema following retinal vein occlusion. The two Phase 3 studies demonstrate replicative results in the ability of ranibizumab to improve in patients with macular edema following retinal vein occlusion when given intravitreally every four weeks (approximately every 28 days) when compared to sham treatment.

(b) (4)

(b) (4)

9.2 Recommendation on Regulatory Action

It is recommended that this supplemental Biologics License Application be approved with labeling revisions identified in this review.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

9.3.2 Required Phase 4 Commitments

Genentech commits to the following postmarketing commitments:

1. Submit the clinical study reports (CSRs) from the 6 month observation periods for Study FVF4165g and FVF4166g by October 1, 2010.

2. Submit the CSR from Study FVF3426g by November 1, 2011.

3. Provide safety and efficacy data on at least 150 patients with macular edema following a retinal vein occlusion, followed for at least 15 months and randomized sometime within 15 months of their first treatment with Lucentis. Patients must receive 7 monthly doses of Lucentis, be evaluated monthly for the need of additional doses of Lucentis based on OCT and visual acuity criteria and if determined to not need an additional monthly dose of Lucentis be randomized to receive an additional dose or not to receive an additional dose of Lucentis.

    a. Protocol submitted to FDA: November 1, 2010
    b. Study Start (First Patient In): March 1, 2011
    c. CSR Submission: October 1, 2013

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

Refer to Appendix 10.2

9.5 Comments to Applicant

Investigator discrepancy should be clarified.

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

Following is the most recent approved labeling from Supplement 044 with the applicant's proposed changes submitted in this supplemental BLA 053.

Applicant's deletions are noted by ~~strikethrough~~ and insertions by underline.
Reviewer's deletions are noted by ~~strikethrough~~ and insertions by underline.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

FINAL SIGNATURES:

NAME	SIGNATURE	DATE
Rhea A. Lloyd, MD Medical Officer		6/22/2010
William M. Boyd, MD Clinical Team Leader		6/22/2010
Wiley A. Chambers, MD Acting Division Director		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

CHEMISTRY REVIEW(S)

Gorski, Lori M

From: Pohlhaus, Timothy
Sent: Wednesday, March 03, 2010 5:29 PM
To: Gorski, Lori M
Cc: CDER-TB-EER; Pohlhaus, Timothy
Subject: TB-EER response STN 125156/S-053

Attachments: 125156s53 TB- EER response.doc; 125156s53 TB- EER form 3-2-10.doc

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Genentech's STN 125156/S-053. Please see the attached response for the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 125156/S-053 at this time.

125156s53
ER response.(

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
lding 51, Room 3218
er Spring, MD 20993
one - (301) 796-5224

From: Gorski, Lori M
Sent: Tuesday, March 02, 2010 4:23 PM
To: CDER-TB-EER
Subject: TB-EER Form BLA 125156/S-053

<< File: 125156s53 TB- EER form 3-2-10.doc >>

125156s53
ER form 3-2-

Please let me know if you need anything further.

Lori Gorski
Project Manager
Division of Anti-Infective & Ophthalmology Products
Phone 301-796-0722
Fax 301-796-9881
mail lori.gorski@fda.hhs.gov

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: June 22, 2010

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125156/S-053
Product: Lucentis (ranibizumab injection)
Short summary of application:

New Indication - Additional indication for the treatment of Macular Edema Following Retinal Vein Occlusion

---

FACILITY INFORMATION

Manufacturing Location: USA
Firm Name: Genentech
Address: 1 DNA Way, South San Francisco, CA, 94080-4990
FEI: 2917293
Short summary of manufacturing activities performed: drug substance

Inspected August 18-21, 2009 by SAN-DO and classified NAI. The CBI profile was updated and is considered acceptable.

Manufacturing Location: (b) (4)

---

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: drug product mfg

Inspected (b) (4) by IOG and classified NAI. The (b) (4) profiles were updated and are considered acceptable.

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: drug product release testing

Inspected (b) (4) by IOG and classified VAI. The laboratory system was covered. The site was also inspected (b) (4) by CDER-DMPQ as a (b) (4) for (b) (4) and classified VAI. This inspection covered drug product release testing.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Bethesda, MD 20892
Tel. 301-827-0850

Memorandum of Review

Date: April 6, 2010

To: File for STN: 125156/53

From: Sarah Kennett, Ph.D.

Through: Chana Fuchs, Ph.D., Team Leader

Subject: sBLA for 125156 (immunogenicity assay validation associated with the RVO indication supplement)

Applicant: Genentech

Product: Ranibizumab (Lucentis)

Filing Action Date: Feb. 20, 2010 **Status:** Filed

Action Due Date: June 22, 2010

Review Recommendation: The ELISA assay, FBV.013, is acceptable for assessing formation of anti-ranibizumab antibodies in the retinal vein occlusion (RVO) subjects.

Review Comments:

A new assay, FBV.013, has been implemented for assessing formation of anti-drug antibodies in the retinal vein occlusion (RVO) subjects. The previous assays were submitted in the original BLA submission (Dec. 30, 2005) and amendment 17 in response to PMC 3 (Sept. 28, 2007; cross referenced from IND 8633). The ECLA assays developed in response to PMC3 use technology that is no longer available. The new assay, a bridging ELISA was validated in study FBV.013.AVR_0. The presence of antibodies in the initial bridging assay is confirmed by repeating the assay in the presence of an excess of unlabeled ranibizumab. Confirmed positives are characterized by titration. The Agency agreed that testing for neutralizing antibodies was not required if the anti-ranibizumab antibody rates were not higher in the RVO studies than in previous studies (July 23, 2009 pre-meeting package response).

The assay for anti-ranibizumab antibodies is a bridging ELISA. Samples and controls are (b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

[redacted]

[redacted]

Conclusions:

I. Recommendation: The ELISA assay, FBV.013, is acceptable for assessing formation of anti-ranibizumab antibodies in the retinal vein occlusion (RVO) subjects.

II. Sections Deferred to other reviewers: None. This review pertains only to the immunogenicity assay validation.

III. Post-marketing commitments: None

IV. Future Inspection Items: None

cc:

RPM:	Lori Gorski, RPM
OBP Drive:	via M. Welschenbach
DMA Drive:	BLA (STN: 125156)
DMA Paper Files:	BLA (STN: 125156)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

STATISTICAL REVIEW(S)

May 20, 2010

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125156/S-053
Drug Name:	Lucentis® (ranibizumab injection)
Indication(s):	Treatment of macular edema following retinal vein occlusion (RVO)
Applicant:	Genentech
Date(s):	Submitted: December 22, 2009
	PDUFA due date: June 22, 2010
Review Priority:	Priority
Biometrics Division:	IV
Statistical Reviewer:	Dongliang Zhuang, PhD
Concurring Reviewer:	Yan Wang, PhD
Medical Division:	Anti-infectives/Ophthalmology
Clinical Team:	Rhea Lloyd, MD; William Boyd, MD; Wiley Chambers, MD
Project Manager:	Lori Gorski

Keywords: macular edema, branch retinal vein occlusion, central retinal vein occlusion, best corrected visual acuity

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Lucentis® (ranibizumab injection) was approved on June 30, 2006 for the treatment of neovascular (wet) age-related macular degeneration (AMD). This supplemental Biologics License Application (sBLA) seeks the revision of the Lucentis U.S. Package Insert (USPI) to include the new indication for the treatment of macular edema following retinal vein occlusion (RVO).

Studies FVF4165g and FVF4166g formed the bases of the sBLA. The studies demonstrated that, for subjects with either branch RVO (BRVO) or central RVO (CRVO), monthly administration of ranibizumab at 0.3-mg or 0.5-mg dose led to statistically significant improvement in visual acuity compared to sham-treated subjects. The improvement was seen as early as 7 days after the first injection and continued through Month 6.

Table 1 shows the mean change from baseline in visual acuity scores and the percentage of subjects who gained ≥ 15 letters in visual acuity in the study eye at 6 months.

Table 1: Mean Change from Baseline in Visual Acuity Scores and Gain of ≥ 15 Letters in the Study Eye at 6 Months (Randomized Subjects; Study FVF4165g and Study FVF4166g)

Study	Treatment	Number of Subjects Randomized	Mean (SD): Number of Letters	LS Mean Difference (vs. Sham)	Gain of ≥ 15 Letters
FVF4165g	Sham	132	7.3 (13.0)		28.8%
	0.3-mg	134	16.6 (11.0)	9.4	55.2%
	0.5-mg	131	18.3 (13.2)	10.6	61.1%
FVF4166g	Sham	130	0.8 (16.2)		16.9%
	0.3-mg	132	12.7 (15.9)	11.5	46.2%
	0.5-mg	130	14.9 (13.2)	13.8	47.7%

LS = least squares; Derived from a pairwise ANOVA models adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).
Source: FVF4165g CSR Tables 18 and 19; FVF4166g CSR Tables 17 and 18.

In Study FVF4165g, subjects treated with 0.3-mg and 0.5-mg ranibizumab had an average increase of +16.6 letters and +18.3 letters from baseline in visual acuity score in the study eye, respectively, compared with +7.3 letters for the subjects treated with sham injection. In Study FVF4166g, subjects treated with 0.3-mg and 0.5-mg ranibizumab had a mean change of +12.7 letters and +14.9 letters from baseline in visual acuity score in the study eye, respectively, compared with +0.8 letters for the subjects treated with sham injection. For both studies, the

comparison between each of the ranibizumab groups and the sham group had a p-value < 0.0001 after adjusting for multiplicity.

A greater percentage of subjects in the ranibizumab groups gained ≥ 15 letters in visual acuity at 6 months compared to sham group. The difference between each of the ranibizumab groups and the sham group in the proportion of subjects gaining ≥ 15 letters in visual acuity at 6 months was statistically significant for both studies.

The benefits of ranibizumab were also demonstrated by the decline of the central foveal thickness. Statistically significant difference between each of the ranibizumab groups and the sham group in the mean change from baseline in central foveal thickness was observed as early as Day 7 and was maintained through Month 6.

Based on the results from Studies FVF4165g and FVf4166g, the Reviewer recommends the revision of the Lucentis U.S. Package Insert (USPI) to include the indication for the treatment of macular edema following retinal vein occlusion (RVO).

1.2 Brief Overview of Clinical Studies

Ranibizumab was evaluated in two pivotal clinical studies (FVF4165g and FVF4166g) in subjects with macular edema following RVO. The studies, conducted in the United States, are ongoing at the time of application submission. This application was supported by the data from the 6-month treatment period. At the time of analyses, all subjects had either completed the visit at 6 months or discontinued early from the study.

Both studies are Phase III, multicenter, randomized, double-masked, sham injection-controlled trials. The studies consist of a 28-day screening period (Days -28 to -1) and a 6-month treatment period, followed by a 6-month observation period. Subjects received their first intravitreal ranibizumab injection or sham injection on Day 0. At subsequent monthly visits, subjects were evaluated for safety and efficacy by the evaluating physician prior to receiving an injection of ranibizumab or sham. After the 6-month treatment period, all subjects will continue to be monitored for safety and efficacy outcomes at each monthly visit for the remainder of the 12-month period. During the 6-month observation period (beginning at the Month 6 visit), all subjects will be evaluated monthly to determine the need for retreatment with ranibizumab. The primary efficacy endpoint for the studies is the mean change from baseline in best corrected visual acuity (BCVA) score at 6 months, based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at a starting test distance of 4 meters.

Subjects 18 years of age or older with macular edema secondary to BRVO were eligible to participate in Study FVF4165g. Study FVF4165g enrolled a total of 397 subjects from 93

investigative sites. Subjects were randomized in a 1:1:1 ratio to one of three treatment groups, with 132 subjects in the sham group, 134 subjects in the 0.3-mg ranibizumab group, and 131 subjects in the 0.5-mg ranibizumab group. A total of 376 subjects (94.7%) completed Month 6 of the study.

Subjects 18 years of age or older with macular edema secondary to CRVO were eligible to participate in Study FVF4166g. Study FVF4166g enrolled a total of 392 subjects from 95 investigative sites. Subjects were randomized in a 1:1:1 ratio to one of three treatment groups, with 130 subjects in the sham group, 132 subjects in the 0.3-mg ranibizumab group, and 130 subjects in the 0.5-mg ranibizumab group. A total of 363 subjects (92.6%) completed Month 6 of the study.

The two trials are almost identical in treatment schedule, study assessments, and primary and secondary efficacy endpoints. However, there in one difference between the two studies in design. Study FVF4165g allowed rescue treatment for the treated eyes with laser photocoagulation in all three treatment arms starting at Month 3 or Month 9 if the evaluating physician determined that the rescue laser treatment was necessary based on predetermined rescue criteria. Study FVF4166g did not allow rescue treatment.

1.3 Statistical Issues and Findings

According to the statistical analysis plan, an analysis of variance (ANOVA) was used to analyze the primary efficacy endpoint, the mean change from baseline in BCVA score at 6 months. The ANOVA model included treatment and baseline visual acuity score strata ($\leq$ 34 letters, 35–54 letters, and $\geq$ 55 letters). All pairwise comparisons between each ranibizumab group and the sham injection group were performed using a statistical model that included only two treatment groups at a time. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for multiplicity. Analysis of the primary efficacy endpoint was based on the intent-to-treat (ITT) population. Missing values were imputed using the last-observation-carried-forward (LOCF) method. The Reviewer found the Applicant's analyses of the primary efficacy endpoint acceptable.

The Reviewer conducted additional analyses to examine the robustness of the results from the Applicant's analysis. The first analysis used an ANOVA model that was the same as the Applicant's model. But the analysis included all three treatment groups and the pairwise comparisons between each ranibizumab group and the sham injection group were derived from the same model. The second analysis employed a mixed model for repeated measure (MMRM) analysis based on the observed data. This analysis provided an alternative way of analyzing the data without relying on the LOCF approach to handle missing data. The results from these analyses are consistent with those from the Applicant's analysis.

2. INTRODUCTION

2.1 Overview

This sBLA seeks the addition to the Lucentis U.S. Package Insert (USPI) of the new indication for the treatment of macular edema following retinal vein occlusion (RVO), based on the clinical data from two pivotal studies.

2.1.1 Class and Indication

According to the Applicant's submission, RVO is the second leading cause of blindness in patients with retinal vascular disease after diabetic retinopathy. The incidence of RVO in the United States in 2007 was estimated to be 180,000, with 144,000 patients diagnosed with BRVO and 36,000 diagnosed with CRVO.

Currently, the only approved therapy for the treatment of macular edema following BRVO or CRVO is Ozurdex™ (Approved on June 17, 2009), a sustained-release intravitreal implant containing dexamethasone. Ozurdex™ is associated with the increase in intraocular pressure (IOP) relative to sham-treated patients, a well-recognized side effect of intravitreal corticosteroid therapy. In addition, the use of Ozurdex™ is contraindicated in patients with advanced glaucoma; there are currently no drug therapies indicated for treatment of macular edema following RVO in patients with advanced glaucoma.

Ranibizumab is a recombinant, humanized monoclonal IgG1 antibody antigen-binding fragment that selectively binds to and neutralizes the biologic activities of all known isoforms of human vascular endothelial growth factor-A (VEGF-A; also referred to as VEGF), as well as the proteolytic cleavage product VEGF. Ranibizumab's clinical development was focused on VEGF-mediated retinal diseases, and clinical benefit has been demonstrated in neovascular (wet) age-related macular degeneration (AMD), with approval granted for this indication on 30 June 2006. The rationale for the use of ranibizumab in the treatment of patients with RVO is supported by its mechanism of action of neutralizing the biologic activity of VEGF, which results in the reduction of vascular permeability and macular edema, hallmarks of RVO.

2.1.2 History of Drug Development

The development of Ranibizumab for the indication of macular edema following RVO was conducted under BB-IND 8633.

A Type C meeting via teleconference was held on January 29, 2007 to discuss the clinical development plan of ranibizumab for the treatment of macular edema secondary to RVO. At the meeting and during the subsequent communications following protocol reviews, the Agency recommended against the use of sham injection as the primary control and suggested the use of

at least three doses in the studies to demonstrate dose response and a full understanding of the safety and efficacy of ranibizumab in this patient population. However, the Applicant was convinced that the studies, if successful, would provide adequate data to support labeling of ranibizumab for the RVO indication. The selection of the 0.3-mg and 0.5-mg ranibizumab doses was driven mainly by the Applicant's desire to leverage the wealth of safety and efficacy data in the AMD clinical program. The Applicant did not consider the benefits and risks of including ranibizumab doses either higher or lower than 0.3 mg and 0.5 mg appropriate. To ensure masking and reduce bias, the Applicant proposed to use separate treating and evaluating physicians.

The Applicant requested a Type B meeting, scheduled for July 13, 2009 to discuss the sBLA submission. The Agency provided preliminary responses. In the response, the Agency reiterated the concerns related to the use of the sham injection as the control. Because the Applicant considered further clarification of the Agency's responses unnecessary, the planned meeting was cancelled.

2.1.3 Studies Reviewed

This submission included data from two clinical studies, Study FVF4165 and Study FVF4166g. Subjects 18 years of age or older with macular edema secondary to BRVO or CRVO were eligible to participate in the studies. Both studies were Phase III, multicenter, randomized, double-masked, sham injection-controlled trials. The primary objectives of the studies were to evaluate the efficacy of intravitreal injections of ranibizumab administered monthly for 6 months in the improvement of visual acuity as measured by the mean change in best corrected visual acuity (BCVA) at 6 months compared with baseline, and to evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly for 6 months, followed by a 6-month observation period.

Study FVF4165g enrolled a total of 397 subjects with macular edema secondary to BRVO from 93 investigative sites in the United States. Subjects were randomized in a 1:1:1 ratio to one of three treatment groups, with 132 subjects in the sham group, 134 subjects in the 0.3-mg ranibizumab group, and 131 subjects in the 0.5-mg ranibizumab group. At Month 3 and thereafter, if the evaluating physician determined that the rescue laser treatment was necessary based on rescue criteria, rescue treatment with laser photocoagulation was allowed in all three treatment arms.

Study FVF4166g enrolled a total of 392 subjects with macular edema secondary to CRVO from 95 investigative sites in the United States. Subjects were randomized in a 1:1:1 ratio to one of three treatment groups, with 130 subjects in the sham group, 132 subjects in the 0.3-mg ranibizumab group, and 130 subjects in the 0.5-mg ranibizumab group.

A study schema is presented in Figure 1 to show the treatment and assessment schedule. Rescue treatment of the study eye with laser starting at the Month 3 or 9 visits in Study FVF4165g was omitted from the schema.

Figure 1: Study Schema

Month	0	1	2	3	4	5	6	7	8	9	10	11	12
	Treatment Period						Observation Period						
Sham arm (n=130)	x	x	x	x	x	x	X	X	X	X	X	X	
0.3-mg ranibizumab arm (n=130)	X	X	X	X	X	X	X	X	X	X	X	X	
0.5-mg ranibizumab arm (n=130)	X	X	X	X	X	X	X	X	X	X	X	X	
							1° EP						

x=sham injection; X=0.3-mg or 0.5-mg intravitreal ranibizumab injection; X=ranibizumab injection (if indicated); 1°EP=primary endpoint.

X	Observation period (Months 6–11) retreatment criteria (study eye) for treatment with ranibizumab
Subject's best corrected visual acuity (BCVA) is 20/40 or worse (Snellen equivalent) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts or subject has mean central subfield thickness ≥ 250 µm on OCT.	

2.2 Data Sources

The sBLA submission, including the Applicant's study reports and data sets for the clinical studies are available on EDR at "\\cbsap58\m\eCTD_Submissions\STN125156\0001".

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Endpoints

The primary efficacy outcome measure was the mean change from baseline in BCVA score at 6 months in the study eye based on the ETDRS visual acuity chart and assessed at a starting test

distance of 4 meters. Only one eye was chosen as the study eye. If both eyes were eligible, the eye with the worse visual acuity assessed at screening was selected for study treatment unless the investigator deemed the other eye to be more appropriate based on medical reasons. Only the study eye was treated with either ranibizumab injection or sham injection.

The secondary efficacy outcome measures for the treatment period of the study included:

- Proportion of subjects who gained ≥ 15 letters in BCVA score at 6 months compared with baseline
- Proportion of subjects who lost < 15 letters in BCVA score at 6 months compared with baseline
- Mean change from baseline in BCVA score over time up to 6 months
- Proportion of subjects with a central foveal thickness of ≤ 250 μm, assessed on Optical Coherence Tomography (OCT), at 6 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Four analysis populations were defined in the statistical analysis plan and three of them were relevant to this review. They are: the intent-to-treat (ITT) population, the per-protocol (PP) population, and the safety-evaluable population.

ITT Population

The ITT population included all subjects who were randomized in the study. Treatment groups for this population were defined according to the treatment assigned at randomization. The efficacy analyses were based on this population.

Per-Protocol Population

The per-protocol population included randomized subjects who were considered sufficiently compliant with the protocol. To be included in the per-protocol population, it required that the subject:

- Had non-missing BCVA scores for the study eye at both baseline and Month 6
- Had no violations of any study entry eligibility criteria that were not approved by the Sponsor
- Had not received the wrong study drug or incorrect dose at any time prior to Month 6

- Had not missed three or more study drug treatments for reasons other than protocol-specified treatment holding prior to Month 6
- Had not received any excluded concomitant treatment prior to Month 6
- Had not had treatment assignment unmasked to subject, to masked study site personnel, or to masked study team members at any time at or prior to the Month 6 visit

Treatment groups for this population were defined according to the treatment assigned at randomization.

Safety-Evaluable Population

The safety-evaluable population included randomized subjects who received at least one injection of study drug (ranibizumab or sham) during the 6-month treatment period. Treatment groups for this population were defined according to the actual treatment received as follows:

- Sham: subjects who received only sham injections (i.e., no active treatment) during the 6-month treatment period
- 0.3-mg ranibizumab: subjects who received at least one 0.3-mg ranibizumab injection but no 0.5-mg ranibizumab injections during the 6-month treatment period
- 0.5-mg ranibizumab: subjects who received at least one 0.5-mg ranibizumab injection during the 6-month treatment period

Table 2 presents the subject disposition and primary reasons for discontinuation during the 6-month treatment period for Studies FVF4165g and FVF4166g.

Of 397 subjects enrolled in Study FVF4165g, a total of 376 subjects (94.7%) completed the study through Month 6. There was 1 subject (11403) in the sham group and 1 subject (16603) in the 0.5-mg group who did not receive any study drug. Overall, 21 subjects (5.3%) discontinued from the study prior to Month 6. The most common reason for the study discontinuation was subject's decision. The sham group had a higher discontinuation rate than the ranibizumab groups.

Subject 11009, a 78-year-old non-Hispanic White male in the 0.5-mg ranibizumab group, died during the study. The subject received his first dose of ranibizumab on (b) (4) and the last (b) (4) On (b) (4) the subject experienced severe cerebral hemorrhage. On (b) (4) 8 days after onset of the cerebral hemorrhage, the subject died. The investigator considered the cerebral hemorrhage to be related to study drug. Other suspected causes for the event included concurrent illness.

Subject 14913, a 69-year-old non-Hispanic White male in the 0.5-mg ranibizumab group, discontinued from the study before Month 6 because of the herpes zoster oticus. The investigator

considered the herpes zoster oticus not related to study drug. Other suspected causes for the event included concurrent illness.

Of 392 subjects enrolled in Study FVF4166g, a total of 363 subjects (92.6%) completed the study through Month 6. One subject (34209) in the sham group and 1 subject (37108) in the 0.5-mg group did not receive any study drug. Overall, 29 subjects (7.4%) discontinued from the study prior to Month 6. The most common reasons for the study discontinuation were physician's decision and subject's decision. The sham group had a higher discontinuation rate than the ranibizumab groups.

Five subjects (30304, 36803, 36702, 40502, and 41701) in the sham group discontinued from the study prior to Month 6 visit because of adverse events. These events included worsening of central retinal vein occlusion in the study eye (subject 30304), worsening of central retinal vein occlusion and iris neovascularization and iritis in the study eye (subject 36803), macular edema in the study eye (subject 36702), hip fracture after a fall (subject 40502), and hypertensive retinopathy in the fellow eye (subject 41701). These events were considered not related to study treatment by the investigators.

Subject 30201 in the 0.5-mg ranibizumab group discontinued from the study due to an event of coronary artery disease, which was considered not related to study treatment by the investigators.

Table 2: Subject Disposition and Primary Reason for Discontinuation during the 6-Month Treatment Period (Randomized Subjects; Study FVF4165g and Study 4166g)

	Study FVF 4165g			Study FVF 4166g		
		Ranibizumab			Ranibizumab	
Category	Sham (n=132)	0.3 mg (n=134)	0.5 mg (n=131)	Sham (n=130)	0.3 mg (n=132)	0.5 mg (n=130)
Intent-to-Treat (Randomized)	132 (100%)	134 (100%)	131 (100%)	130 (100%)	132 (100%)	130 (100%)
Per-Protocol Population	109 (82.6%)	111 (82.8%)	106 (80.9%)	104 (80.0%)	118 (89.4%)	102 (78.5%)
Safety-evaluable Population	131 (99.2%)	134 (100%)	130 (99.2%)	129 (99.2%)	132 (100%)	129 (99.2%)
Completed study through Month 6	123 (93.2%)	128 (95.5%)	125 (95.4%)	115 (88.5%)	129 (97.7%)	119 (91.5%)
Discontinued study prior to Month 6	9 (6.8%)	6 (4.5%)	6 (4.6%)	15 (11.5%)	3 (2.3%)	11 (8.5%)
Adverse event	0	0	1 (0.8%)	5 (3.8%)	0	1 (0.8%)
Death	0	0	1 (0.8%)	0	0	0
Lost to follow-up	0	1 (0.7%)	0	0	1 (0.8%)	2 (1.5%)
Physician's decision	1 (0.8%)	1 (0.7%)	3 (2.3%)	5 (3.8%)	1 (0.8%)	4 (3.1%)
Subject's decision	7 (5.3%)	4 (3.0%)	1 (0.8%)	5 (3.8%)	1 (0.8%)	4 (3.1%)
Subject's condition mandated other therapeutic intervention	1 (0.8%)	0	0	0	0	0

Source: Tables 3 and 6 in Applicant's CSRs FVF4165g and FVF4166g.

Demographics are summarized in Table 3. The three treatment groups were balanced in terms of baseline demographics. The majority of the randomized subjects were White, and slightly more than half were male.

Table 4 summarizes key baseline ocular characteristics of the study eye in Studies FVF4165g and FVF4166g. Baseline visual acuity, on average, was worse in subjects in Study FVF4166g than in Study FVF4165g. The mean visual acuity score in the study eye at baseline was 53-56 letters (or, in terms of the approximate Snellen equivalent, a median of 20/63 to 20/80) across all three treatment groups in Study FVF4165g. In Study FVF4166g, the mean visual acuity score at baseline was 47-49 letters (or, in terms of the approximate Snellen equivalent, a median of 20/100) across the three treatment groups. Approximately 10%–16% of subjects in Study FVF4165g and 27%-31% of subjects in Study FVF4166g had a Snellen equivalent of 20/200 or worse at baseline. The mean time from diagnosis of RVO to screening across the three treatment groups was similar: 3.3-3.7 months in Study FVF4165g and 2.9-3.6 months in Study FVF4166g. Overall, the three treatment groups were fairly well balanced with respect to ocular characteristics of the study eye.

Table 3: Demographics (Randomized Subjects; Study FVF4165g and Study 4166g)

	Study FVF 4165g			Study FVF 4166g		
		Ranibizumab			Ranibizumab	
Demographics	**Sham (n=132)**	**0.3 mg (n=134)**	**0.5 mg (n=131)**	**Sham (n=130)**	**0.3 mg (n=132)**	**0.5 mg (n=130)**
Age (year)						
Mean (SD)	65.2 (12.7)	66.6 (11.2)	67.5 (11.8)	65.4 (13.1)	69.7 (11.6)	67.6 (12.4)
Range	26-89	43-90	41-91	20-91	38-90	40-91
Age Group (year); n (%)						
<45	8 (6.1%)	5 (3.7%)	4 (3.1%)	10 (7.7%)	5 (3.8%)	5 (3.8%)
45 to <65	59 (44.7%)	51 (38.1%)	51 (38.9%)	50 (38.5%)	36 (27.3%)	46 (35.4%)
65 to <85	60 (45.5%)	74 (55.2%)	69 (52.7%)	67 (51.5%)	80 (60.6%)	71 (54.6%)
≥85	5 (3.8%)	4 (3.0%)	7 (5.3%)	2 (2.3%)	11 (8.3%)	8 (6.2%)
Sex; n (%)						
Male	74 (56.1%)	67 (50.0%)	71 (54.2%)	72 (55.4%)	71 (53.8%)	80 (61.5%)
Female	58 (43.9%)	67 (50.0%)	60 (45.8%)	58 (44.6%)	61 (46.2%)	50 (38.5%)
Ethnicity; n (%)						
Hispanic or Latino	9 (6.8%)	11 (8.2%)	7 (5.3%)	15 (11.5%)	16 (12.1%)	10 (7.7%)
Not Hispanic or Latino	121 (91.7%)	117 (87.3%)	122 (93.1%)	113 (86.9%)	115 (87.1%)	117 (90.0%)
Not Available	2 (1.5%)	6 (4.5%)	2 (1.5%)	2 (1.5%)	1 (0.8%)	3 (2.3%)
Race [a]; n (%)						
American Indian or Alaska Native	2 (1.5%)	2 (1.5%)	0	1 (0.8)	0	1 (0.8%)
Asian	6 (4.5%)	1 (0.7%)	5 (3.8%)	6 (4.6%)	3 (2.3%)	6 (4.6%)
Black or African American	13 (9.8%)	11 (8.2%)	13 (9.9%)	8 (6.2%)	16 (12.1%)	10 (7.7%)
Native Hawaiian or other Pacific Islander	0	0	0	0	0	2 (1.5)
White	108 (81.8%)	112 (83.6%)	107 (81.7%)	113 (86.9%)	108 (81.8%)	108 (83.1%)
Not Available	4 (3.0%)	9 (6.7%)	6 (4.6%)	3 (2.3%)	5 (3.8%)	5 (3.8%)

Source: Table 7 in Applicant's CSRs FVF4165g and FVF4166g.

Table 4: Baseline Ocular Characteristics of the Study Eye (Randomized Subjects; Study FVF4165g and Study FVF4166g)

Characteristic	Study FVF4165g			Study FVF4166g		
		Ranibizumab			Ranibizumab	
	Sham (n=132)	0.3 mg (n=134)	0.5 mg (n=131)	Sham (n=130)	0.3 mg (n=132)	0.5 mg (n=130)
Months since diagnosis of RVO						
Mean (SD)	3.7 (3.7)	3.6 (4.1)	3.3 (3.1)	2.9 (2.9)	3.6 (3.2)	3.3 (3.7)
Range	0.0–16.0	0.0–35.0	0.0–13.0	0.0–14.0	0.0–12.0	0.0–27.0
Visual acuity						
Number of letters (0–100)						
Mean (SD)	54.7 (12.2)	56.0 (12.1)	53.0 (12.5)	49.2 (14.7)	47.4 (14.8)	48.1 (14.6)
Range	16–73	25–73	22–79	16–71	9–72	21–73
Distribution, n						
≤34	9 (6.8%)	9 (6.7%)	13 (9.9%)	26 (20.0%)	33 (25.0%)	30 (23.1%)
35–54	50 (37.9%)	48 (35.8%)	49 (37.4%)	49 (37.7%)	46 (34.8%)	50 (38.5%)
≥55	73 (55.3%)	77 (57.5%)	69 (52.7%)	55 (42.3%)	53 (40.2%)	50 (38.5%)
Approximate Snellen equivalent						
Median	20/80	20/63–20/80	20/80	20/100	20/100	20/100
Distribution, n						
20/200 or worse	14 (10.6%)	14 (10.4%)	21 (16.0%)	35 (26.9%)	41 (31.1%)	39 (30.0%)
Better than 20/200 but worse than 20/40	99 (75.0%)	99 (73.9%)	95 (72.5%)	83 (63.8%)	82 (62.1%)	84 (64.6%)
20/40 or better	19 (14.4%)	21 (15.7%)	15 (11.5%)	12 (9.2%)	9 (6.8%)	7 (5.4%)

CSR=clinical study report; RVO=retinal vein occlusion.
Source: CSR FVF4165g, Table 8, and CSR FVF4166g, Table 8.

3.1.3 Statistical Methodologies

This application was supported by the data from the 6-month treatment period. At the time of analyses, all subjects had either completed the visit at Month 6 or discontinued early from the study.

Analyses of the primary and secondary efficacy endpoints were based on the intent-to-treat (ITT) population, including all randomized subjects. Subjects were grouped according to their randomized treatment. Missing values were imputed using the last-observation-carried-forward (LOCF) method for the primary and secondary efficacy endpoints.

Subject randomization was stratified by study center and the Day 0 BCVA score (≤34 letters [approximately worse than 20/200], 35–54 letters [approximately 20/200 to worse than 20/80], or ≥55 letters [approximately 20/80 or better]) based on the ETDRS chart and assessment at a starting test distance of 4 meters. A dynamic randomization method was used to obtain an approximately 1:1:1 ratio between the three treatment arms.

The primary efficacy endpoint, the mean change from baseline in BCVA score at 6 months, was compared between each ranibizumab group and the sham injection group using an ANOVA model including treatment and baseline visual acuity score strata (≤ 34 letters, 35−54 letters, and ≥ 55 letters). An unstratified analysis was performed as a sensitivity analysis. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for multiplicity arising from the comparison of the two ranibizumab groups with the sham injection group. Specifically, if the p-values for both comparisons were ≤ 0.05, then both ranibizumab groups was considered statistically significantly different from the sham injection group. If the p-value for the comparison of one ranibizumab group with the sham injection group was > 0.05, the other ranibizumab group was considered statistically significantly different from the sham injection group only if the p-value for the comparison was ≤ 0.025.

Among the secondary efficacy outcome measures for the treatment period of the study, the mean change from baseline in BCVA score over time up to 6 months was analyzed in the same way as the primary efficacy endpoint.

Analysis of covariance (ANCOVA) models, including treatment, baseline visual acuity score strata (≤ 34 letters, 35-54 letters, and ≥ 55 letters), and the baseline value of the corresponding endpoint, were used to analyze the following continuous endpoints:

- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months

- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months

Cochran-Mantel-Haenszel (CMH) χ^2 tests were used to compare the proportion of subjects between treatment groups for binary endpoints. These included the proportion of subjects who gained $\geq$ 15 letters in BCVA score at 6 months compared with baseline, and the proportion of subjects with a central foveal thickness of $\leq$ 250 μm, assessed on OCT, at 6 months. Based on the masked data review, the Applicant anticipated that the proportion of subjects who lost fewer than 15 letters in BCVA score at Month 6 compared with baseline to be high. As a result, the proportion of subjects who lost < 15 letters in BCVA score at 6 months compared with baseline was analyzed using Fisher's exact test.

Provided that a given ranibizumab dose group was statistically different from the control group in the primary endpoint, the secondary efficacy endpoints based on the 6-month treatment period would be tested comparing that ranibizumab dose group with the control group. A hierarchical testing approach that included the Hochberg-Bonferroni multiple comparison procedure within each stage of the hierarchy was used to manage the type I error rate for the testing of multiple secondary efficacy endpoints.

3.1.4 Results and Conclusions

3.1.4.1 Visual Acuity Endpoints

Both study demonstrated statistically significant difference between each of the ranibizumab groups and the sham group in the mean change from baseline in BCVA score at 6 months. The analysis of the mean change from baseline in visual acuity scores in the study eye at 6 months is presented in Table 5 and Table 6 for Study FVF4165g and Study FVF4166g, respectively.

At Month 6 of Study FVF4165g, subjects treated with 0.3-mg and 0.5-mg ranibizumab had an average increase of +16.6 letters and +18.3 letters from baseline in visual acuity score in the study eye, respectively, compared with +7.3 letters for the subjects treated with sham injection. The comparison between each of the ranibizumab groups and the sham group has a p-value < 0.0001 after adjusting for multiplicity.

The study allowed subjects to receive laser treatment in the study eye starting at the Month 3 visit if the subjects experienced a continued loss of vision compared with the visit 3 months prior to the current visit. Approximately 55% of sham-treated subjects and 19% of ranibizumab-treated subjects in Study FVF4165g received rescue laser treatment in the study eye at any time during the 6-month treatment period. Despite a higher percentage of application of laser rescue

treatment in subjects treated with the sham injection, the treatment benefit of the ranibizumab compared with the sham injection remains significant.

Table 5: Mean Change from Baseline in Visual Acuity Scores in the Study Eye at 6 Months (Randomized Subjects; Study FVF4165g)

		Ranibizumab	
Visual Acuity at Month 6	Sham (n=132)	0.3 mg (n=134)	0.5 mg (n=131)
Number of letters change from baseline			
Mean (SD)	7.3 (13.0)	16.6 (11.0)	18.3 (13.2)
95% CI for mean [a]	(5.1, 9.5)	(14.7, 18.5)	(16.0, 20.6)
Difference in LS means (vs. sham) [b]		9.4	10.6
95% CI for difference [b]		(6.6, 12.2)	(7.6, 13.6)
p-value (vs. sham) [b]		<0.0001	<0.0001

ANOVA=analysis of variance; LS=least squares.

Note: The last-observation-carried-forward method was used to impute missing data.

[a] Derived from the t-distributions.

[b] Based on pairwise ANOVA models adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).

Source: CSR FVF4165g, Table 18.

Table 6: Mean Change from Baseline in Visual Acuity Scores in the Study Eye at 6 Months (Randomized Subjects; Study FVF4166g)

	No. of Subjects		
		Ranibizumab	
Visual Acuity at Month 6	Sham (n=130)	0.3 mg (n=132)	0.5 mg (n=130)
Number of letters change from baseline			
Mean (SD)	0.8 (16.2)	12.7 (15.9)	14.9 (13.2)
95% CI for mean [a]	(-2.0, 3.6)	(9.9, 15.4)	(12.6, 17.2)
Difference in LS means (vs. sham) [b]		11.5	13.8
95% CI for difference [b]		(7.7, 15.3)	(10.3, 17.4)
p-value (vs. sham) [b]		<0.0001	<0.0001

ANOVA=analysis of variance; CI=confidence interval; LS=least squares.

Note: The last-observation-carried-forward method was used to impute missing data.

[a] Derived from the t-distributions.

[b] Based on pairwise ANOVA models adjusted for baseline visual acuity score (≤34, 35–54, ≥55 letters).

Source: CSR FVF4166g, Table 17.

At Month 6 of Study FVF4166g, subjects treated with 0.3-mg and 0.5-mg ranibizumab had a mean change of +12.7 letters and +14.9 letters from baseline in visual acuity score in the study eye, respectively, compared with +0.8 letters for the subjects treated with sham injection. The comparison between each of the ranibizumab groups and the sham group is statistically significant (p-value < 0.0001).

In the Applicant's analysis, all pairwise comparisons between each ranibizumab group and the sham injection group were performed using a statistical model that included only two treatment groups at a time. A more common approach is to derive the pairwise difference from a model that includes all treatment groups. The Reviewer conducted a separate analysis to include all the data from the three treatment groups. The results from this analysis are almost identical to that of the Applicant's analysis.

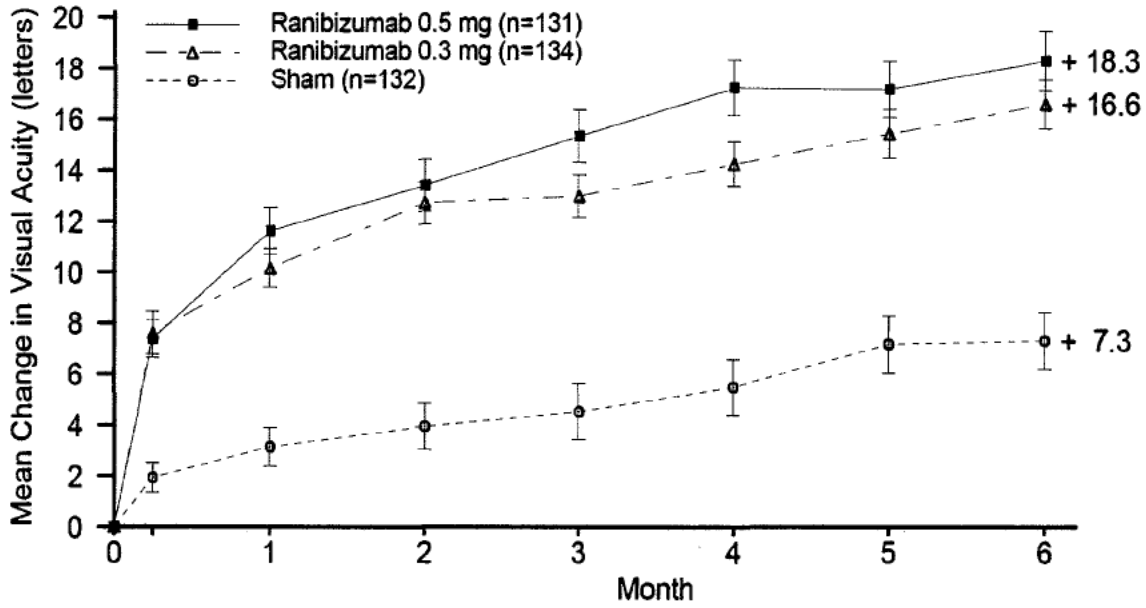
Subject randomization was stratified by study center and the Day 0 BCVA score. When study center is included in the model, the results are comparable to those from the Applicant's primary efficacy analyses, which excluded study center from the model.

Both studies had good retention. Among the subjects in the sham group, 0.3-mg ranibizumab group, and 0.5-mg ranibizumab group, the number and percentage of subjects who had missing Month 6 visual acuity score for the study eye was 11(8.3%), 8(6.0%), and 8(6.1%) in Study FVF4165g, and 19(14.6%), 9(6.8%), and 19(14.6%) in Study FVF4166g. The Applicant's sensitivity analyses using the observed data without imputation of the missing data yielded results that were generally consistent with those from the primary analyses.

A mixed model for repeated measure (MMRM) analysis based on the observed data provides an alternative way to analyze the data without relying on the LOCF approach to handle missing data. Based on the Reviewer's analysis, the results from this analysis are consistent with those from the Applicant's analysis.

Figure 2 and Figure 3 show the mean change from baseline over time up to 6 months in visual acuity in the study eye for the two studies. The treatment benefit of ranibizumab in improving visual acuity compared to the sham control was observed as early as 7 days after the first injection and continued through Month 6.

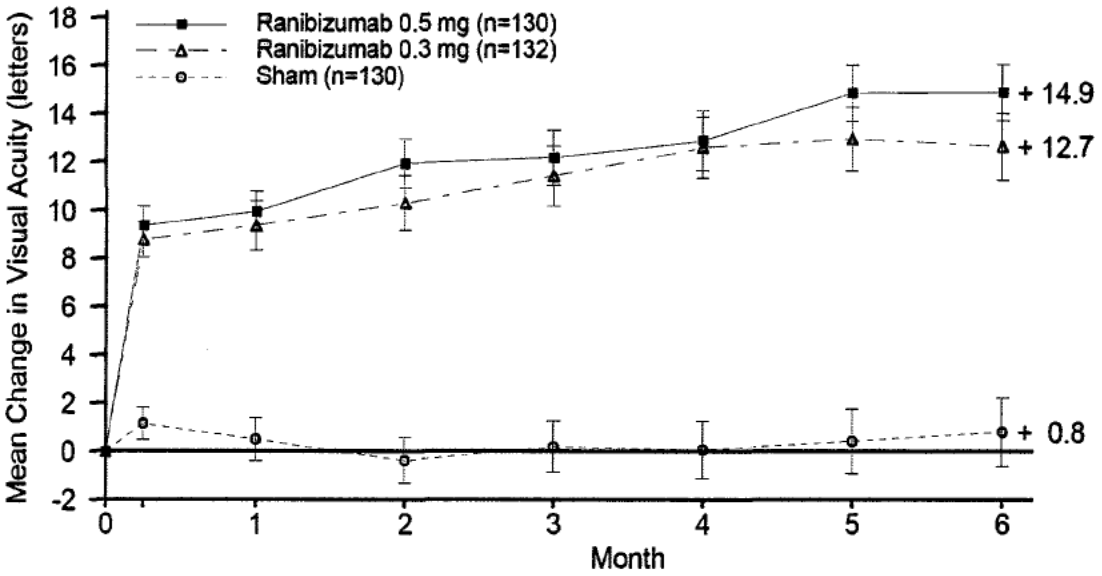
Figure 2: Mean Change from Baseline in Visual Acuity of the Study Eye (Randomized Subjects, Study FVF4165g)



Note: The last-observation-carried-forward method was used to impute missing data.
Vertical bars are ±1 standard error of the mean.

Source: CSR FVF4165g, Figure 2.

Figure 3: Mean Change from Baseline in Visual Acuity of the Study Eye (Randomized Subjects, Study 4166g)



Note: The last-observation-carried-forward method was used to impute missing data.
Vertical bars are ±1 standard error of the mean.

Source: CSR FVF4166g, Figure 2.

Overall, subjects in Study FVF4165g experienced greater increase in BCVA score compared to the subjects in Study FVF4166g. One difference between the two studies was that rescue laser treatment was allowed in Study FVF4165g starting at Month 3. Was the greater change in BCVA score for the study eye in Study FVF4165g attributable to the application of the rescue laser treatment during the study?

Based on the Reviewer's analyses, Table 7 compares the change in BCVA from baseline at Month 6 in the study eye for the subjects who received rescue laser treatment to those who didn't.

During the 6-month treatment period, 54.5% of sham-treated subjects, 18.7% of 0.3-mg ranibizumab-treated subjects, and 19.8% of 0.5-mg ranibizumab-treated subjects in Study FVF4165g received rescue laser treatment in the study eye. For these subjects, the mean changes in BCVA from baseline at Month 6 were 4.7, 13.0 and 15.8 for the sham group, 0.3-mg ranibizumab group and 0.5-mg ranibizumab group, respectively. In comparison, for the subjects who didn't receive rescue laser treatment, the mean changes in BCVA from baseline at Month 6 were 10.4, 19.6 and 16.8 for the sham group, 0.3-mg ranibizumab group and 0.5-mg ranibizumab group, respectively. Therefore, the greater change in BCVA score for the study eye in Study FVF4165g cannot be attributed to the application of the rescue laser treatment.

Table 7: Mean Change from Baseline in Visual Acuity Scores in the Study Eye at 6 Months by Rescue Laser Treatment (Randomized Subjects; Studies FVF4165g)

Treatment	Category	N	Baseline	Change	95% CI for Change
Sham	Received Rescue	72	53.5	4.7	(1.7, 7.7)
	Didn't Receive Rescue	60	56.1	10.4	(7.1, 13.7)
0.3-mg Ranibizumab	Received Rescue	25	49.6	15.8	(10.7, 20.9)
	Didn't Receive Rescue	109	57.5	16.8	(14.7, 18.8)
0.5-mg Ranibizumab	Received Rescue	26	51.8	13.0	(7.9, 18.1)
	Didn't Receive Rescue	105	53.3	19.6	(17.1, 22.1)

Source: Primary reviewer's analysis.

During the discussion of the clinical development plan for ranibizumab in RVO, the Agency raised the concern about the validity of the sham injection as a control. Compared to sham injection, the intravitreal injection is associated with alteration in fluid concentration, increased inflammation, and needle reaction. When these factors or the lack of these factors lead to the subject's cognizance of his or her treatment assignment, bias could arise in his or her assessment. Nevertheless, it is impossible to ascertain whether the subject recognized his or her treatment for the study eye. What was known to the subjects in both studies is the fact that the fellow eye was

not treated. Therefore, the data from the untreated fellow eye could be used as reference for the examination of the subject's response to the assessment for the study eye.

Table 8 compares the change in BCVA from baseline at Month 6 between the study eye and the fellow eye within each treatment group. Baseline visual acuity, on average, was worse in subjects in Study FVF4166g than in Study FVF4165g for study eye, but it was comparable for fellow eye.

Table 8: Mean Change from Baseline in Visual Acuity Scores in the Study Eye and Fellow Eye at 6 Months (Randomized Subjects; Studies FVF4165g and FVF4166g)

		Study FVF4165g		Study FVF4166g	
Treatment	**Category**	**Study Eye**	**Fellow Eye**	**Study Eye**	**Fellow Eye**
Sham	Baseline	54.7	79.8	49.2	78.9
	Change from Baseline	+7.3	+1.2	+0.8	+0.2
0.3-mg Ranibizumab	Baseline	56.0	79.4	47.4	80.0
	Change from Baseline	+16.6	+1.8	+12.7	+1.1
0.5-mg Ranibizumab	Baseline	53.0	81.4	48.1	78.8
	Change from Baseline	+18.3	+2.5	+14.9	+0.2

Source: Primary reviewer's analysis.

For untreated fellow eyes, the changes from baseline in BCVA score at Month 6 were small and similar among three treatment groups in both studies. Specifically, for subjects in 0.3-mg ranibizumab, 0.5-mg ranibizumab, and sham group, the changes in BCVA score from baseline at Month 6 were 1.8, 2.5, and 1.2 in Study FVF4165g, and they were 1.1, 0.2, and 0.2 in Study FVF4166g.

The change in BCVA score was 0.8 for the study eye in the sham group in Study FVF4166g, which was comparable to that observed for the fellow eye (0.2). However, the change in BCVA score is notably different (7.3 vs. 1.8) between the study eye and the fellow eye for subjects in the sham group in Study FVF4165g even though neither eye received active treatment.

The analyses presented in Table 7 and Table 8 could not give a definite answer as to whether there was bias in the subject's assessment. They could not explain the greater change in BCVA in Study FVF4165g, either. However, they showed the consistency in subject's assessment of the fellow eye and the similarity in BCVA change between the sham-treated eye and the fellow eye in Study FVF4166g, which provide further support to the validity of the studies.

Other endpoints related to visual acuity included the proportion of subjects who gained 15 or more letters (approximately 3 lines) at 6 months compared with baseline (Table 9 and Table 10) and the proportion of subjects who lost fewer than 15 letters at 6 months.

Table 9: Proportion of Subjects Gaining ≥ 15 Letters in Visual Acuity from Baseline at Month 6 in the Study Eye (Randomized Subjects, Study FVF 4165g)

		Ranibizumab	
Visual Acuity at Month 6	**Sham (n=132)**	**0.3 mg (n=134)**	**0.5 mg (n=131)**
Gain of ≥ 15 letters from baseline			
n (%)	38 (28.8%)	74 (55.2%)	80 (61.1%)
95% CI for percentage [a]	(21.1%, 36.5%)	(46.8%, 63.6%)	(52.7%, 69.4%)
Percent difference (vs. sham) [b]		26.8%	31.3%
95% CI of the difference [b]		(15.6%, 38.0%)	(20.1%, 42.6%)
p-value (vs. sham) [c]		< 0.0001	< 0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
a. By normal approximation.
b. Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) using Cochran–Mantel–Haenszel weights.
c. From Cochran–Mantel–Haenszel χ^2 tests adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).
Source: CSR FVF4165g, Table 19.

Table 10: Proportion of Subjects Gaining ≥ 15 Letters in Visual Acuity from Baseline at Month 6 in the Study Eye (Randomized Subjects, Study FVF4166g)

		Ranibizumab	
Visual Acuity at Month 6	**Sham (n=130)**	**0.3 mg (n=132)**	**0.5 mg (n=130)**
Gain of ≥ 15 letters from baseline			
n (%)	22 (16.9%)	61 (46.2%)	62 (47.7%)
95% CI for percentage [a]	(10.5%, 23.4%)	(37.7%, 54.7%)	(39.1%, 56.3%)
Percent difference (vs. sham) [b]		29.3%	30.3%
95% CI of the difference [b]		(18.8%, 39.7%)	(19.6%, 40.9%)
p-value (vs. sham) [c]		< 0.0001	< 0.0001

Note: The last-observation-carried-forward method was used to impute missing data.
a. By normal approximation.
b. Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) using Cochran–Mantel–Haenszel weights.
c. From Cochran–Mantel–Haenszel χ^2 tests adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).
Source: CSR FVF4166g, Table 18.

A greater percentage of subjects in the ranibizumab groups gained ≥ 15 letters in visual acuity at Month 6 compared to sham group. The difference between each of the ranibizumab groups and

the sham group in the proportion of subjects gaining ≥ 15 letters in visual acuity at Month 6 was statistically significant for both studies.

In both studies, the proportion of subjects who lost fewer than 15 letters in BCVA score at Month 6 compared with baseline was high. In Study FVF4165g, 100% of subjects in the 0.3-mg ranibizumab group and 98.5% in the 0.5-mg ranibizumab group compared with 95.5% of subjects in the sham group lost fewer than 15 letters in BCVA score at Month 6. In Study FVF4166g, the proportion of subjects who lost fewer than 15 letters in BCVA score at Month 6 was 96.2% for the 0.3-mg ranibizumab group, 98.5% for the 0.5-mg ranibizumab group, and 84.6% for the sham group.

3.1.4.2 Central Foveal Thickness

Central foveal thickness was defined as the center point thickness, as assessed on OCT. In both studies, a clinically meaningful and statistically significant decrease in central foveal thickness was observed in ranibizumab-treated subjects compared with sham treatment by the first post-baseline scheduled OCT measurement at Day 7. Decreases in central foveal thickness generally continued and were maintained over 6 months with monthly dosing. At Month 6, the 0.3-mg and 0.5-mg ranibizumab groups had a mean decrease of 337.3 and 345.2 μm respectively, compared to a decrease of 157.7 μm for the sham group in Study FVF4165g; whereas a mean decrease of 433.7 μm, 452.3 μm, and 167.7 μm was observed for the 0.3-mg ranibizumab group, 0.5-mg ranibizumab group, and sham group in Study FVF4166g.

At Month 6, 91% of subjects in the 0.3-mg ranibizumab group and 85% of subjects in the 0.5-mg ranibizumab group had central foveal thickness ≤ 250 μm compared with 45.5% of subjects in the sham group in Study FVF 4165g. In Study FVF4166g, 75% of subjects in the 0.3-mg ranibizumab group and 77% of subjects in the 0.5-mg ranibizumab group had a central foveal thickness ≤ 250 μm compared with 23% of subjects in the sham group. In both studies, the difference between each of the ranibizumab groups and the sham group in the proportion of subjects with a central foveal thickness ≤ 250 μm at 6 months was statistically significant (pvalue < 0.0001).

The proportion of subjects with central foveal thickness ≤ 250 μm at 6 months and the mean change from baseline in central foveal thickness at 6 months are summarized in Table 11 and Table 12.

Table 11: Central Foveal Thickness in the Study Eye at Month 6
(Randomized Subjects, Study FVF4165g)

Central Foveal Thickness at Month 6	Sham (n=132)	Ranibizumab 0.3 mg (n=134)	Ranibizumab 0.5 mg (n=131)
≤250 μm			
n (%)	60 (45.5%)	122 (91.0%)	111 (84.7%)
95% CI for percentage [a]	(37.0%, 53.9%)	(86.2%, 95.9%)	(78.6%, 90.9%)
Difference in % (vs. sham) [b]		45.5%	40.1%
95% CI for difference [b]		(36.0%, 55.0%)	(29.9%, 50.2%)
p-value (vs. sham) [c]		<0.0001	<0.0001
Change from baseline (μm)			
Mean (SD)	−157.7 (224.2)	−337.3 (224.4)	−345.2 (238.2)
95% CI for mean [d]	(−196.3, −119.1)	(−375.6, −298.9)	(−386.4, −304.0)
Difference in LS means (vs. sham) [e]		−148.7	−134.8
95% CI for difference [e]		(−183.6, −113.8)	(−172.7, −96.8)
p-value (vs. sham) [e]		<0.0001	<0.0001

ANCOVA=analysis of covariance; LS=least squares.

Note: Central foveal thickness was defined as the center point thickness. The last-observation-carried-forward method was used to impute missing data.

[a] By normal approximation.

[b] Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) using Cochran–Mantel–Haenszel weights.

[c] From Cochran–Mantel–Haenszel χ^2 tests adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).

[d] Derived from the t-distributions.

[e] Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) and baseline value of central foveal thickness.

Source: CSR FVF4165g, Table 20.

Table 12: Central Foveal Thickness in the Study Eye at Month 6
(Randomized Subjects, Study FVF4166g)

Central Foveal Thickness at Month 6	No. of Subjects		
		Ranibizumab	
	Sham (n=130)	0.3 mg (n=132)	0.5 mg (n=130)
≤250 μm			
n	30 (23.1%)	99 (75.0%)	100 (76.9%)
95% CI for percentage [a]	(15.8%, 30.3%)	(67.6%, 82.4%)	(69.7%, 84.2%)
Percent difference (vs. sham) [b]		51.9%	54.0%
95% CI for the difference [b]		(41.6%, 62.3%)	(44.0%, 64.1%)
p-value (vs. sham) [c]		<0.0001	<0.0001
Change from baseline (μm)			
n	129	131	130
Mean (SD)	–167.7 (308.4)	–433.7 (295.9)	–452.3 (257.6)
95% CI for mean [d]	(–221.5, –114.0)	(–484.9, –382.6)	(–497.0, –407.6)
Difference in LS means (vs. sham) [e]		–272.2	–283.8
95% CI for difference [e]		(–329.9, –214.5)	(–337.8, –229.8)
p-value (vs. sham) [e]		<0.0001	<0.0001

ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares.
Note: Central foveal thickness was defined as the center point thickness.
The last-observation-carried-forward method was used to impute missing data.
[a] By normal approximation.
[b] Weighted estimates adjusted for baseline visual acuity score (≤34, 35–54, ≥55 letters) using Cochran–Mantel–Haenszel weights.
[c] From Cochran–Mantel–Haenszel χ^2 tests adjusted for baseline visual acuity score (≤34, 35–54, ≥55 letters).
[d] Derived from the t-distributions.
[e] Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤34, 35–54, ≥55 letters) and baseline value of central foveal thickness.

Source: CSR FVF4166g, Table 19.

3.1.4.3 Patient-Reported Outcomes

The National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) was used to assess vision-related patient-reported outcomes. The mean changes from baseline over time up to 6 months in two of the NEI VFQ-25 subscales, near activities and distance activities, were evaluated as secondary endpoints. The results are presented in Table 13 and Table 14.

In Study FVF4165g, the improvement in both NEI VFQ-25 near activities subscale score and NEI VFQ-25 distance activities subscale score was observed at Month 6. The improvement was 7.3, 12.1 and 13.7 points for the sham group, 0.3-mg ranibizumab group, and 0.5-mg ranibizumab group, respectively, for the near activities subscale; and 6.3, 10.3, and 11.3 points for the sham group, 0.3-mg ranibizumab group, and 0.5-mg ranibizumab group, respectively, for the distance activities subscale. The treatment effect of ranibizumab versus sham injection for these two subscales at Month 6 was statistically significant.

Table 13: Mean Change from Baseline in the NEI VFQ-25 Near Activities and Distance Activities Subscale Scores at Month 6 (Randomized Subjects, Study FVF4165g)

Change in NEI VFQ-25 Subscale Score at Month 6	Sham (n=129)	Ranibizumab 0.3 mg (n=133)	Ranibizumab 0.5 mg (n=130)
Near activities			
Mean (SD)	7.3 (15.3)	12.1 (17.3)	13.7 (18.0)
95% CI for mean [a]	(4.6, 10.0)	(9.1, 15.1)	(10.6, 16.8)
Difference in LS means (vs. sham) [b]		4.1	6.4
95% CI for difference [b]		(0.6, 7.6)	(3.0, 9.8)
p-value (vs. sham) [b]		0.0214	0.0002
Distance activities			
Mean (SD)	6.3 (15.0)	10.3 (17.2)	11.3 (16.6)
95% CI for mean [a]	(3.7, 8.9)	(7.3, 13.2)	(8.4, 14.2)
Difference in LS means (vs. sham) [b]		3.8	5.1
95% CI for difference [b]		(0.5, 7.0)	(2.0, 8.3)
p-value (vs. sham) [b]		0.0248	0.0014

ANCOVA=analysis of covariance; LS=least squares.

Note: The last-observation-carried-forward method was used to impute missing data.

[a] Derived from the t-distributions.

[b] Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) and baseline value of the corresponding endpoint.

Source: CSR FVF4166g, Table 21.

Statistically significant improvement in both NEI VFQ-25 near activities subscale score and NEI VFQ-25 distance activities subscale score was also observed at Month 6 in Study FVF4166g. The improvement was 5.1, 10.2 and 9.3 points for the sham group, 0.3-mg ranibizumab group, and 0.5-mg ranibizumab group, respectively, for the near activities subscale; and 2.8, 8.9, and 6.7 points for the sham group, 0.3-mg ranibizumab group, and 0.5-mg ranibizumab group, respectively, for the distance activities subscale.

Table 14: Mean Change from Baseline in the NEI VFQ-25 Near Activities and Distance Activities Subscale Scores at Month 6 (Randomized Subjects, Study FVF4166g)

Change in NEI VFQ-25 Subscale Score at Month 6	Sham (n=127)	Ranibizumab 0.3 mg (n=130)	Ranibizumab 0.5 mg (n=128)
Near activities			
Mean (SD)	5.1 (17.1)	10.2 (17.4)	9.3 (18.1)
95% CI for the mean [a]	(2.1, 8.1)	(7.1, 13.2)	(6.1, 12.5)
Difference in LS means (vs. sham) [b]		5.8	4.9
95% CI for the difference [b]		(2.1, 9.4)	(1.2, 8.6)
p-value (vs. sham) [b]		0.0019	0.0099
Distance activities			
Mean (SD)	2.8 (15.6)	8.9 (13.7)	6.7 (16.3)
95% CI for the mean [a]	(0.0, 5.5)	(6.5, 11.2)	(3.8, 9.5)
Difference in LS means (vs. sham) [b]		6.3	4.1
95% CI for the difference [b]		(3.1, 9.5)	(0.7, 7.6)
p-value (vs. sham) [b]		0.0002	0.0199

ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares;
NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25.

Note: The last-observation-carried-forward method was used to impute missing data.

[a] Derived from the t-distributions.

[b] Based on pairwise ANCOVA models adjusted for baseline visual acuity score (≤34, 35−54, ≥55 letters) and baseline value of the corresponding endpoint.

Source: CSR FVF4166g, Table 20.

(b) (4)

According to SEALD review, there is limited evidence to suggest that a change in near vision activities and distance vision activities subscales of 7 to 12.5 points may be clinically relevant. However, it is difficult to pinpoint an exact number from this range that might be clinically relevant. Therefore, the responder was defined according to the cutoff values of 7.0, 8.3 and 12.5, respectively. In Study FVF4165g, a mean change of 7.3 points in near activities and a mean

change of 6.3 points in distance activities were observed in the sham group at 6 months. A 12.5-point change would represent, for example, a 1-category (25-point) improvement in 3 of 6 scale items. An 8.3-point change would represent, for example, a 1-category improvement in 2 of 6 scale items.

Table 15 and Table 16 present the results from the responder analyses of the near activities subscale and the distance activities subscale, respectively. The statistical comparisons between the ranibizumab groups and the sham group were less significant (i.e., larger p-values) than the treatment comparisons based on the change from baseline. For the analyses based on the cutoff value of 12.5 points, the statistical significance between 0.5-mg ranibizumab group and the sham group was not demonstrated.

Table 15: Responder analysis for NEI VFQ-25 Near Activities (Randomized Subjects, Studies FVF4165g and FVF4166g)

	Study FVF4165g			Study FVF4166g		
		Ranibizumab			Ranibizumab	
Category	Sham (n=129)	0.3 mg (n=133)	0.5 mg (n=130)	Sham (n=127)	0.3 mg (n=130)	0.5 mg (n=128)
Gain of ≥ 7 in near activities from baseline						
n (%)	66 (51.2%)	77 (57.9%)	86 (66.2%)	51 (41.2%)	70 (53.9%)	66 (51.6%)
95% CI for percentage [a]	(42.5%, 60.0%)	(49.5%, 66.3%)	(58.0%, 74.3%)	(31.6%, 48.9%)	(45.3%, 62.4%)	(42.9%, 60.2%)
Percent difference (vs. sham) [b]		6.5%	15.5%		14.8%	12.5%
95% CI of the difference [b]		(-5.4%, 18.4%)	(3.7%, 27.3%)		(3%, 26.6%)	(0.5%, 24.4%)
p-value (vs. sham) [c]		0.2863	0.0111		0.0168	0.0436
Gain of ≥ 8.3 in near activities from baseline						
n (%)	65 (50.4%)	77 (57.9%)	85 (65.4%)	51 (41.2%)	69 (53.1%)	66 (51.6%)
95% CI for percentage [a]	(41.8%, 59.0%)	(49.5%, 66.3%)	(57.2%, 73.6%)	(31.6%, 48.9%)	(44.5%, 61.7%)	(42.9%, 60.2%)
Percent difference (vs. sham) [b]		7.3%	15.5%		14.0%	12.5%
95% CI of the difference [b]		(-4.6%, 19.2%)	(3.6%, 27.3%)		(2.2%, 25.8%)	(0.5%, 24.4%)
p-value (vs. sham) [c]		0.2326	0.0116		0.0239	0.0436
Gain of ≥12.5 in near activities from baseline						
n (%)	51 (39.5%)	63 (47.4%)	64 (49.2%)	41 (32.3%)	56 (43.1%)	53 (41.4%)
95% CI for percentage [a]	(31.1%, 48.0%)	(38.9%, 55.9%)	(40.6%, 57.8%)	(24.2%, 40.4%)	(34.6%, 51.6%)	(32.9%, 49.9%)
Percent difference (vs. sham) [b]		7.7%	9.8%		11.8%	9.9%
95% CI of the difference [b]		(-4.2%, 19.7%)	(-2.3%, 21.8%)		(0.3%, 23.3%)	(-1.8%, 21.6%)
p-value (vs. sham) [c]		0.2326	0.1146		0.0495	0.0982

Note: The last-observation-carried-forward method was used to impute missing data.

a. By normal approximation.

b. Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) using Cochran–Mantel–Haenszel weights.

c. From Cochran–Mantel–Haenszel χ^2 tests adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).

Source: primary reviewer's analysis.

Table 16: Responder analysis for NEI VFQ-25 Distance Activities (Randomized Subjects, Studies FVF4165g and FVF4166g)

	Study FVF4165g			Study FVF4166g		
		Ranibizumab			Ranibizumab	
Category	Sham (n=129)	0.3 mg (n=133)	0.5 mg (n=130)	Sham (n=127)	0.3 mg (n=130)	0.5 mg (n=128)
Gain of ≥ 7 in distance activities from baseline						
n (%)	52 (40.3%)	72 (54.1%)	79 (60.8%)	39 (30.7%)	68 (52.3%)	54 (42.2%)
95% CI for percentage [a]	(31.9%, 48.4%)	(45.7%, 62.6%)	(52.4%, 69.2%)	(22.7%, 38.7%)	(43.7%, 60.9%)	(33.6%, 50.7%)
Percent difference (vs. sham) [b]		13.9%	20.3%		21.6%	11.9%
95% CI of the difference [b]		(2.1%, 25.8%)	(8.5%, 32.1%)		(9.8%, 33.3%)	(0.3%, 23.5%)
p-value (vs. sham) [c]		0.0236	0.0011		0.0005	0.0477
Gain of ≥ 8.3 in distance activities from baseline						
n (%)	52 (40.3%)	72 (54.1%)	78 (60.0%)	39 (30.7%)	67 (51.5%)	52 (40.6%)
95% CI for percentage [a]	(31.9%, 48.4%)	(45.7%, 62.6%)	(51.6%, 68.4%)	(22.7%, 38.7%)	(43.0%, 60.1%)	(32.1%, 49.1%)
Percent difference (vs. sham) [b]		13.9%	19.5%		20.9%	10.4%
95% CI of the difference [b]		(2.1%, 25.8%)	(7.7%, 31.3%)		(9.2%, 32.6%)	(-1.1%, 22.0%)
p-value (vs. sham) [c]		0.0236	0.0017		0.0007	0.0811
Gain of ≥12.5 in distance activities from baseline						
n (%)	40 (31.0%)	55 (41.4%)	57 (43.9%)	32 (25.2%)	51 (39.2%)	39 (30.5%)
95% CI for percentage [a]	(23.0%, 39.0%)	(33.0%, 49.7%)	(35.3%, 52.4%)	(17.7%, 32.8%)	(30.8%, 47.6%)	(22.5%, 38.4%)
Percent difference (vs. sham) [b]		10.4%	12.9%		14.5%	5.9%
95% CI of the difference [b]		(-1.1%, 21.9%)	(1.3%, 24.6%)		(3.2%, 25.8%)	(-5.0%, 16.8%)
p-value (vs. sham) [c]		0.0808	0.0319		0.0131	0.2906

Note: The last-observation-carried-forward method was used to impute missing data.

a. By normal approximation.

b. Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) using Cochran–Mantel–Haenszel weights.

c. From Cochran–Mantel–Haenszel χ^2 tests adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).

Source: primary reviewer's analysis.

NEI VFQ-25 scores can be affected by general health status. It is therefore suggested that adjustment for general health should be considered when evaluating treatment efficacy. Table 17 presents the analyses based on ANCOVA models; one model includes the baseline general health score, but the other one doesn't. The results from these two models were comparable, indicating that the NEI VFQ-25 scores were not greatly affected by the general health status in these two studies.

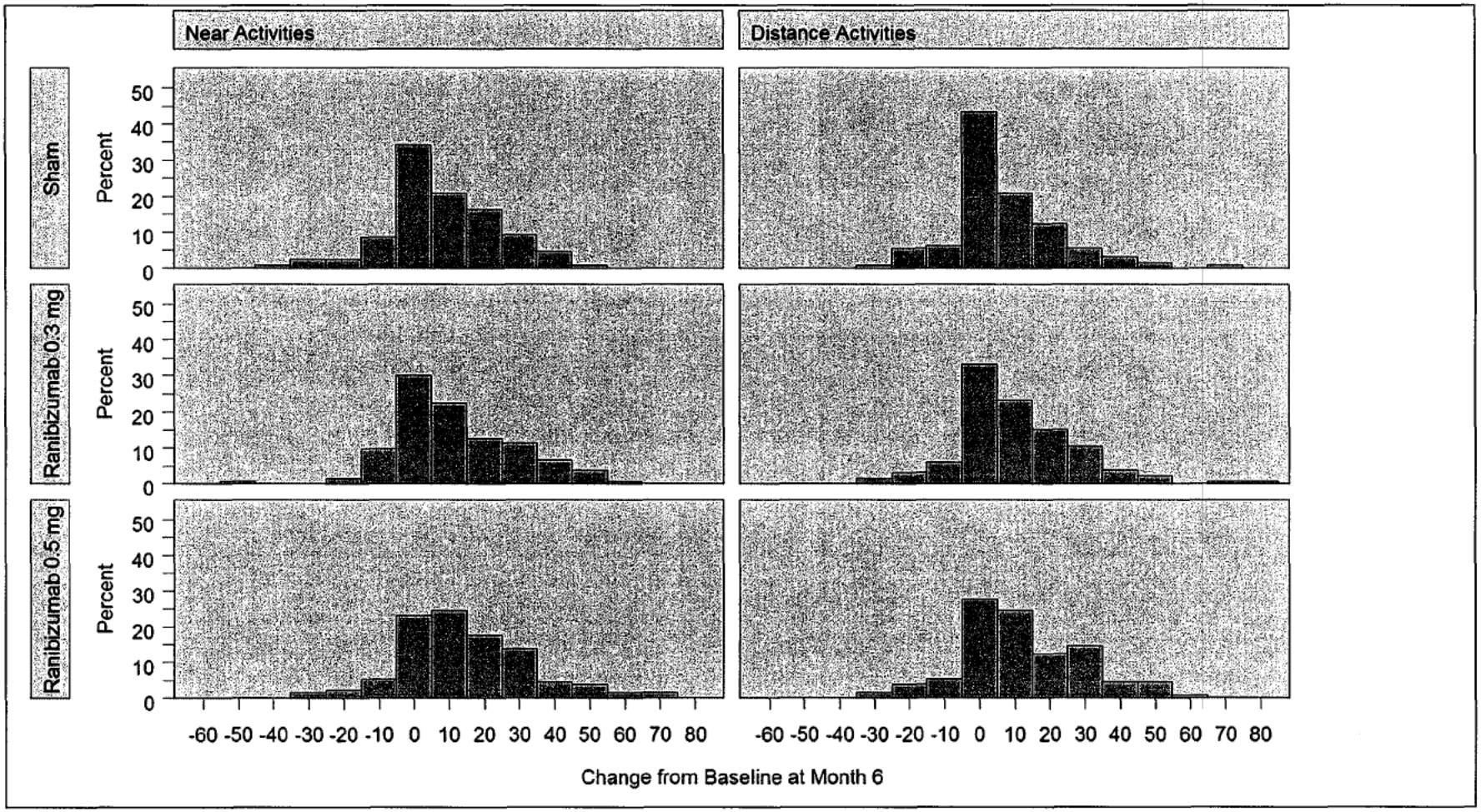
The analyses above, as well as the Applicant's analyses, used parametric methods. The histograms (Figure 4 and Figure 5) of the change from baseline in NEI VFQ-25 near activities and distance activities subscales at 6 Months show that the distributions are skewed to the right. However, due to relatively large sample size, the parametric methods for the treatment comparison are justified.

Table 17: Change from Baseline in NEI VFQ-25 Near Activities and Distance Activities Subscales at 6 Months (Randomized Subjects, Studies FVF4165g and FVF4166g)

Change in NEI VFQ-25 Subscale Scores at Month 6	Study FVF 4165g			Study FVF 4166g		
		Ranibizumab			Ranibizumab	
	Sham (n=129)	0.3 mg (n=133)	0.5 mg (n=130)	Sham (n=127)	0.3 mg (n=130)	0.5 mg (n=128)
Near activities						
Mean (SD)	7.3 (15.3)	12.1 (17.3)	13.7 (18.0)	5.1 (17.1)	10.2 (17.4)	9.3 (18.1)
95% CI for the mean [a]	(4.6, 10.0)	(9.1, 15.1)	(10.6, 16.8)	(2.1, 8.1)	(7.1, 13.2)	(6.1, 12.5)
Difference in LS means (vs. sham) [b]		4.0	6.4		5.9	4.8
95% CI for the difference [b]		(0.6, 7.4)	(3.0, 9.9)		(2.3, 9.6)	(1.2, 8.5)
p-value (vs. sham) [b]		0.0230	0.0003		0.0015	0.0100
Difference in LS means (vs. sham) [c]		3.9	6.2		6.4	5.0
95% CI for the difference [c]		(0.5, 7.3)	(2.8, 9.6)		(2.7, 10.0)	(1.4, 8.7)
p-value (vs. sham) [c]		0.0251	0.0005		0.0006	0.0065
Distance activities						
Mean (SD)	6.3 (15.0)	10.3 (17.2)	11.3 (16.6)	2.8 (15.6)	8.9 (13.7)	6.7 (16.3)
95% CI for the mean [a]	(3.7, 8.9)	(7.3, 13.2)	(8.4, 14.2)	(0.0, 5.5)	(6.5, 11.2)	(3.8, 9.5)
Difference in LS means (vs. sham) [b]		3.7	5.2		6.4	4.1
95% CI for the difference [b]		(0.5, 6.9)	(2.0, 8.4)		(3.1, 9.7)	(0.8, 7.4)
p-value (vs. sham) [b]		0.0230	0.0016		0.0001	0.0154
Difference in LS means (vs. sham) [c]		3.6	5.0		6.9	4.3
95% CI for the difference [c]		(0.5, 6.8)	(1.8, 8.2)		(3.7, 10.1)	(1.1, 7.6)
p-value (vs. sham) [c]		0.0243	0.0023		<0.0001	0.0090

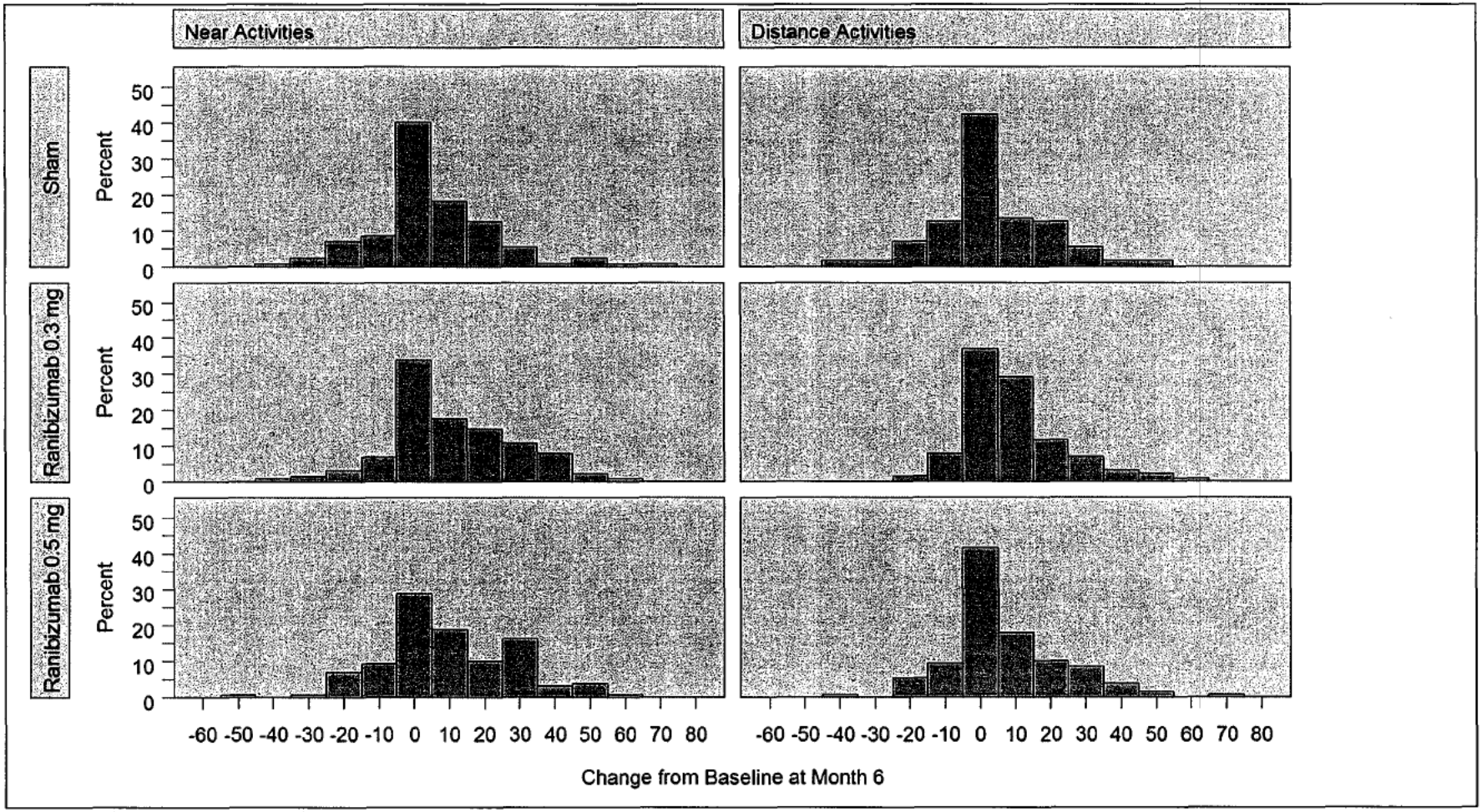
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25.
Note: The last-observation-carried-forward method was used to impute missing data.
a Derived from the t-distributions.
b Based on ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters) and baseline value of the corresponding endpoint.
c Based on ANCOVA models adjusted for baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters), baseline general health score, and baseline value of the corresponding endpoint.
Source: primary reviewer's analysis.

Figure 4: Histograms of Change in NEI VFQ-25 Near Activities and Distance Activities Subscales from Baseline at Month 6 (Randomized Subjects, Study FVF4165g)



Source: primary reviewer's analysis.

Figure 5: Histograms of Change in NEI VFQ-25 Near Activities and Distance Activities Subscales from Baseline at Month 6 (Randomized Subjects, Study FVF4166g)



Source: primary reviewer's analysis.

3.1.4.4 Efficacy Conclusions

For subjects with branch or central RVO, monthly administration of ranibizumab at either 0.3 mg or 0.5 mg dose led to statistically significant improvement in visual acuity compared to sham-treated subjects. The improvement was seen as early as 7 days after the first injection and continued through Month 6. A greater percentage of subjects in the ranibizumab groups gained $\geq$ 15 letters in visual acuity at 6 months compared to sham group.

The benefit of ranibizumab was also demonstrated by the decline of the central foveal thickness. Clinically meaningful and statistically significant difference between each of the ranibizumab groups and the sham group in the mean change from baseline in central foveal thickness was observed as early as Day 7 and was maintained through Month 6.

3.2 Evaluation of Safety

The evaluation of the safety was based on the data collected during the 6-month treatment period.

During the 6-month treatment period, more than 76% of subjects in each treatment group experienced at least one ocular adverse event in the study eye. The most common study eye adverse event was conjunctival hemorrhage, which was experienced by a greater percentage of the subjects in either of the ranibizumab groups (52% and 48%) for the 0.3-mg and 0.5-mg ranibizumab group) than the sham group (37%). Conjunctival hemorrhage was considered to be related to the subconjunctival anesthesia procedure applied to both sham and ranibizumab injections. The penetration of eyes during the ranibizumab injection might have contributed to the higher incidence of conjunctival hemorrhage in the ranibizumab groups compared to sham group.

Eye pain, increased intraocular pressure (IOP), maculopathy, myodesopsia, ocular hyperemia, ocular vascular disorder, retinal depigmentation, retinal exudates, and retinal vascular disorder were also reported more often in the ranibizumab groups compared with the sham group.

In comparison, approximately 23%–28% of subjects experienced at least one adverse event in the fellow eye. The number of events within each adverse event category was low, and there was no notable imbalance between treatment groups.

The frequency of ocular serious adverse events in the study eye was low with 7 and 12 subjects experiencing such events in Study FVF4165g and Study FVF4166g, respectively. The rate was similar among the three treatment groups in Study FVF4165g at approximately 2%. But in Study 4166g, the rate was higher in the sham group (4.7%) than the 0.3-mg (3.0%) and 0.5-mg (1.6%) ranibizumab groups.

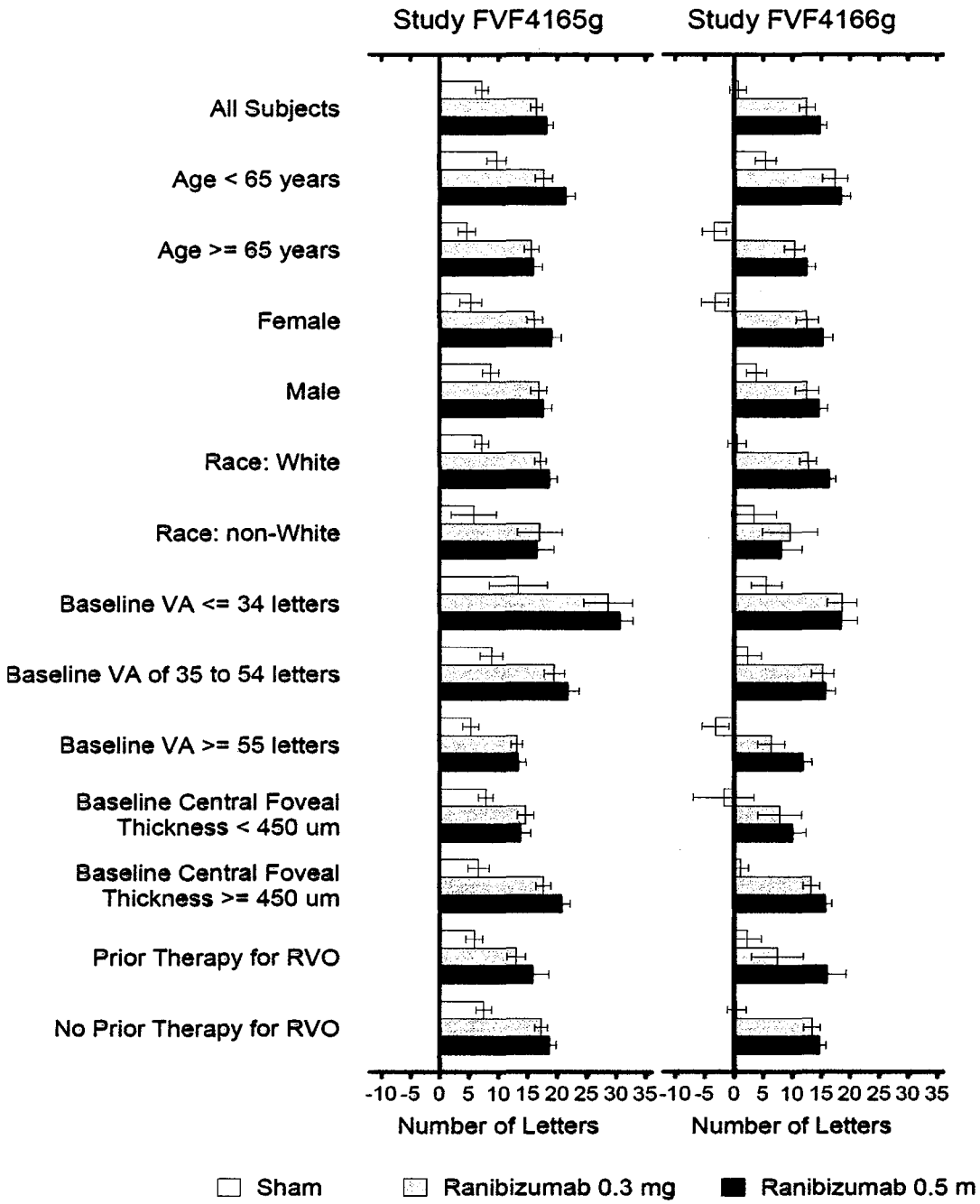
The most common non-ocular adverse event was hypertension. The number of events within each of the remaining adverse event categories was low, and no trends were noted between treatment groups.

A comprehensive safety evaluation can be found in the clinical review by Dr. Rhea Lloyd.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The Applicant presented subgroup analyses of the mean change from baseline in visual acuity score at Month 6 and the proportion of subjects who gained ≥ 15 letters in visual acuity at Month 6 compared with baseline. The subgroups were defined by the following baseline characteristics: age (< 65, ≥ 65 years), sex (male, female), race (White, non-White), baseline visual acuity score in the study eye (≤ 34, 35–54, ≥ 55 letters), central foveal thickness as assessed on OCT in the study eye (< 450 μm, ≥ 450 μm), and any prior therapies for RVO in the study eye (yes, no). The results are presented in Figure 6 and Figure 7. It can be seen that the treatment effect of ranibizumab at doses of either 0.3 mg or 0.5 mg over sham injection among subgroups was consistent with the overall results.

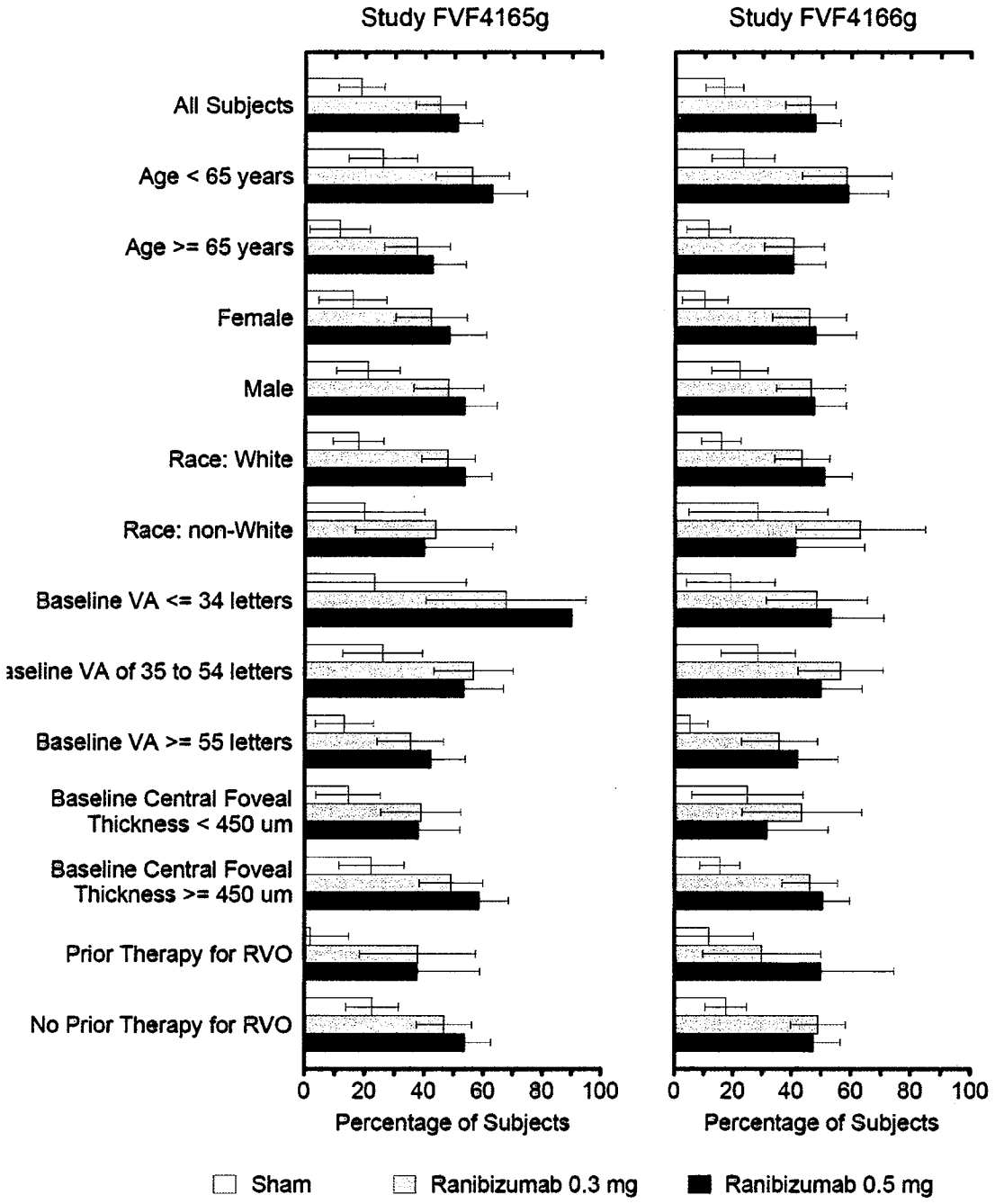
Figure 6: Subgroup Analysis of the Mean Change from Baseline in Visual Acuity Scores in the Study Eye at Month 6 (Randomized Subjects, Studies FVF4165g and FVF4166g)



RVO=retinal vein occlusion; VA=visual acuity.
Notes: Horizontal lines are ±1 standard error of the mean. The last-observation-carried-forward method was used to impute missing data.

Source: ISS, Figure 5.

Figure 7: Subgroup Analysis of the Proportion of Subjects Gaining ≥ 15 Letters in the Study Eye at Month 6 (Randomized Subjects, Studies FVF4165g and FVF4166g)



CI=confidence interval; RVO=retinal vein occlusion; VA=visual acuity.
Notes: Horizontal lines are 95% CI for the percentages based on normal approximation.
The last-observation-carried-forward method was used to impute missing data.

Source: ISS, Figure 5.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The statistical analyses were conducted according to the statistical analysis plan. An analysis of variance (ANOVA) was used to analyze the primary efficacy endpoint, the mean change from baseline in BCVA score at 6 months. The ANOVA model included treatment and baseline visual acuity score strata ($\leq$ 34 letters, 35−54 letters, and $\geq$ 55 letters). All pairwise comparisons between each ranibizumab group and the sham injection group were performed using a statistical model that included only two treatment groups at a time. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for multiplicity. Analysis of the primary efficacy endpoint was based on the intent-to-treat (ITT) population. Missing values were imputed using the last-observation-carried-forward (LOCF) method. The Reviewer found the Applicant's analyses of the primary efficacy endpoint acceptable.

The Reviewer conducted additional analyses to examine the robustness of the results from the Applicant's analysis. The first analysis used an ANOVA model that was the same as the Applicant's model. But the analysis included all three treatment groups and the pairwise comparisons between each ranibizumab group and the sham injection group were derived from the same model. The second analysis employed a mixed model for repeated measure (MMRM) analysis based on the observed data. This analysis provided an alternative way of analyzing the data without relying on the LOCF approach to handle missing data. The results from these analyses are consistent with those from the Applicant's analysis.

It was noted that subjects in Study FVF4165g experienced greater increase in BCVA score compared to the subjects in Study FVF4166g, even though the difference in the treatment effect between each ranibizumab group and the sham group were similar. One difference between the two studies was that rescue laser treatment was allowed in Study FVF4165g starting at Month 3. However, the examination of the data according to rescue laser treatment doesn't indicate that the greater change in BCVA score for the study eye in Study FVF4165g was attributable to the application of the rescue laser treatment during the study.

5.2 Conclusions and Recommendations

For subjects with branch or central RVO, monthly administration of ranibizumab at either 0.3 mg or 0.5 mg dose led to clinically beneficial and statistically significant improvement in visual acuity compared to sham-treated subjects. The improvement was seen as early as 7 days after the first injection and continued through Month 6. A greater percentage of subjects in the ranibizumab groups gained $\geq$ 15 letters in visual acuity at 6 months compared to sham group.

These benefits in visual acuity were also consistent across all subgroups based on a wide range of subject characteristics.

The benefit of ranibizumab was also demonstrated by the decline of the central foveal thickness. Clinically meaningful and statistically significant difference between each of the ranibizumab groups and the sham group in the mean change from baseline in central foveal thickness was observed as early as Day 7 and was maintained through Month 6.

The evaluation of the efficacy from Studies FVF4165g and FVF4166g supports the use of either 0.3 mg or 0.5 mg of ranibizumab administered by monthly intravitreal injection for the treatment of patients with macular edema following either branch RVO or central RVO.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dongliang Zhuang, PhD
Date: May 20, 2010

Statistical Team Leader: Yan Wang, PhD

cc:
HFD-520/Project Manager: Lori Gorski
HFD-520/Medical Officer: Rhea Lloyd, MD
HFD-520/Medical Team Leader: William Boyd, MD
HFD-725/Primary Statistical Reviewer: Dongliang Zhuang, PhD
HFD-725/Statistical Team Leader: Yan Wang, PhD
HFD-725/Biometrics Deputy Division Director: Daphne Lin, PhD
HFD-725/Biometrics Division Director: Mohammad Huque, PhD
HFD-700/Office of Biostatistics: Lillian Patrician

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

OTHER REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 18, 2010

TO: William Boyd, MD, Cross Discipline Team Leader
Division of Anti-Infective and Ophthalmology Products
Jane A. Dean, RN, MSN, Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Jennifer Harris, MD, Clinical Reviewer
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125156/53

APPLICANT: Genentech, Inc.
Contact: Philip Risser, Manager, Clinical Regulatory Affairs
1 DNA Way
South San Francisco, California 94080-4990
650 225 4524 (Office)
650 892 3594 (BlackBerry)
risser.philip@gene.com

DRUG: Lucentis® (ranibizumab injection)

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS: Treatment of patients with macular edema secondary to retinal vein occlusion (RVO)

CONSULTATION REQUEST DATE: February 1, 2010

PDUFA: June 22, 2010

I. BACKGROUND:

The sponsor, Genentech Inc., submitted supplemental Biologics License Application (sBLA) application for Lucentis® (ranibizumab injection) (BLA 125156/53). The purpose of this supplemental Biologics License Application (sBLA) was to support revision of the Lucentis Package Insert (PI) to include the new indication Macular Edema Following Retinal Vein Occlusion (RVO). This was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application.

Lucentis® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Lucentis® (ranibizumab injection) was originally approved on 30 June 2006 by the FDA for the treatment of patients with neovascular age-related macular degeneration (AMD). To support approval, the Applicant has provided data from two well-controlled pivotal studies (Study FVF4165g and Study FVF4166g), which they believe provide sufficient evidence for the safety and efficacy of Lucentis® (ranibizumab injection) for treatment of patients with macular edema following RVO. This sBLA has received a priority review designation because of the existence of an unmet medical need for a treatment modality for patients with macular edema following RVO.

Protocols inspected:

The protocols inspected were Protocol FVF4165g and Protocol FVF4166g. Both protocols were similar in design and were phase III, multicenter, randomized, double-masked, sham injection–controlled study of the efficacy and safety of intravitreal ranibizumab compared with sham injections in subjects with macular edema.

Protocol FVF4165g was done in subjects with macular edema secondary to branch retinal vein occlusion (BRVO) while Protocol FVF4166g was done in subjects with macular edema secondary to central retinal vein occlusion (CRVO). Subjects were included in the study if they were e ≥ 18 years of age with foveal center–involved macular edema secondary to BRVO (Study FVF4165g) or CRVO (StudyFVF4166g).

Subjects had to have a BRVO (Study FVF4165g) or CRVO (StudyFVF4166g) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts of 20/40 to 20/400 (Snellen equivalent) and a mean central subfield thickness ≥ 250 μm on two optical coherence tomography (OCT) measurements (at screening and Day 0) in the study eye.

Study FVF4165g planned to enroll 397 subjects from 93 investigative sites. The study FVF4166g was conducted at 95 investigational sites in the United States that enrolled 392 subjects. In both studies eligible subjects were then randomized in a 1:1:1 ratio to receive 0.5-mg ranibizumab, 0.3-mg ranibizumab, or sham injection once a month. Only one eye was to be

chosen as the study eye. Only the study eye was to be treated with either ranibizumab injection or sham injection. During the 6-month treatment period, subjects were to receive monthly injections of the treatment to which they were randomized (0.5-mg ranibizumab, 0.3-mg ranibizumab, or sham). During the 6-month observation period, all subjects were to be evaluated monthly to determine the need for retreatment with ranibizumab.

Genentech utilized a number of contract research organizations to provide clinical trial services in both studies . (b) (4) was to be responsible for subject randomization and the distribution of study drug. (b) (4) was responsible for study site monitoring, for data entry, and data management. A central reading center, the (b) (4) was to receive all optical coherence tomography (OCT) images, fluorescein angiograms, and fundus photographs for grading and/or storage. A central laboratory, (b) (4) was to analyze hematology, serum chemistry, coagulation, and urine samples. Analyses of samples for antibodies to ranibizumab and serum ranibizumab concentrations were to be performed by Genentech. An external and independent statistical coordinating center, (b) (4) was to be responsible for verifying that subject randomization and monthly study drug kit assignments were conducted correctly.

In both studies, the primary efficacy outcome measure was the mean change from baseline in BCVA score in the study eye at 6 months, with Branch Retinal Vein Occlusion (BCVA) assessed using the (ETDRS) visual acuity chart at a starting distance of 4 meters.

Secondary efficacy outcome measures were to be based on BCVA, central foveal thickness as assessed by OCT, and National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) subscale scores.

Safety measurements included adverse events and physical examaination that were to be 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. In addition to visual acuity measurement, slit-lamp examination, intraocular pressure (IOP) measurement, and dilated binocular high-magnification indirect ophthalmoscopy were the primary methods to be used to assess ocular safety.

Field inspections of this study were important to verify the quality of conduct of the study for this supplement. The two sites were selected for inspection due to enrollment of large numbers of study subjects, numbers of INDs that investigators have participate in, and prior inspectional history.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
S. Young Lee, MD Retina Research Institute of Texas 5441 Health Center Drive Abilene, TX 79606	FVF4165g / 19345 /23	June 11, 2010	Pending Preliminary: NAI
Peter Campochiaro, MD Johns Hopkins Hospital School of Medicine 719 Maumenee 600 N. Wolfe Street Baltimore, MD 21287	FVF4166g / (17521) /14	April 6, 2010-April 16, 2010	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, EIR has not been received and letter has not yet issued to the CI.

1. **S. Young Lee MD**
   Retina Research Institute of Texas
   5441 Health Center Drive
   Abilene, TX 79606

   a. What was inspected?
   This inspection was conducted in accordance with Compliance Program 7348.811 on 6/11/2010.

   A total of 28 subjects were screened and 23 were enrolled and randomized into the study. Twenty-two (22) subjects completed the study. There were no Serious Adverse Events (SAEs) or Deaths during the study. The inspection evaluated informed consent and included review of source documents and hard copy reporting for 100% of subjects randomized. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting, and 5) handling of pharmacokinetic samples. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

   b. General observations/commentary:
   The inspection of Dr. Lee's site revealed that the study was conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

   c. Assessment of data integrity:
   Based on inspectional findings, efficacy and safety data obtained from this site are considered reliable.

   Note: The observations noted above are based on communications with the DSI field investigator; an inspection summary addendum will be generated after reviewing the EIR and if conclusions change upon receipt and review of the EIR.

2. **Peter Campochiaro, MD**
Johns Hopkins Hospital School of Medicine
719 Maumenee
600 N. Wolfe Street
Baltimore, MD 21287

a. **What was inspected**:

This inspection was conducted in accordance with Compliance Program 7348.811 Between April 6, 2010 and April 16, 2010.

A total of 23 subjects were screened and 14 were enrolled and randomized the study. Of the 14 subjects randomized, 13 subjects completed the study. One was withdrawn because subject received a steroid injection into an eye during the study. The inspection included review of records for 14 subjects who were randomized. There were no Serious Adverse Events (SAEs) or Deaths during the study. The following items were reviewed for verification: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequacy of adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**:

3. The inspection of Dr. Peter Campochiaro's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator for failure to follow the investigational plan. The following regulatory violations were observed during the inspection:

- Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. For example:

  Specifically, gonioscopy assessments, follow-up contacts, physical exams and vital signs were not done according to the protocol. (Subject #s 34001, 34002 ,34003, 34004, 34005,34006, 34007,34008,34009, 34010, 34011 ,34012 ,34013)

  DSI Reviewer Comment:

  Per protocol section 4.5.2, gonioscopy assessments were to be completed on every visit between the screening period and month 5; follow-up contacts were to be completed after each injection, starting on day 0, and ending at the end of month 11; physical exams were to be completed on day of screening and month 12; vital signs were to be completed on day of screening, day 0, and every visit except on day 7. This should have been conducted and documented in accordance with the investigational plan; however, the deviations from protocol

were isolated in nature for any given subject throughout the course of the study, and are unlikely to impact data integrity.

c. **Assessment of data integrity**:

Although regulatory violations were noted above, it is unlikely based on the nature of the violations that they significantly affect overall reliability of safety and efficacy data from the site, as they appear to be isolated findings. Based on the provided EIR for this site and Dr. Campochiaro's responses regarding the regulatory violations during the inspection, which were documented in the EIR, data derived from Dr. Campochiaro's site are considered reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on inspection of study related and source documents, the studies appear to have been conducted adequately and the data in support of the BLA appear reliable. The final classification of the inspection for Dr. Campochiaro is VAI. The preliminary classification of the Clinical Investigator inspection for Dr. Lee is NAI.

Note: The observations noted for Dr. Lee's site inspection are based on communications with the DSI field investigator; an inspection summary addendum will be generated after reviewing the EIR and if conclusions change upon receipt and review of the EIR.

/Kassa Ayalew, M.D./
Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

/Tejashri Purohit-Sheth, M.D./
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2010.002.A.00010
APPLICATION NUMBER	BLA 125156
LETTER DATE/SUBMISSION NUMBER	12/18/2009 /S053
PDUFA GOAL DATE	06/22/2010
DATE OF CONSULT REQUEST	01/27/2010
REVIEW DIVISION	Division of Anti-Infective and Ophthalmology Products
MEDICAL REVIEWER	Rhea Lloyd
REVIEW DIVISION PM	Lori Gorski
SEALD REVIEWER(S)	Päivi Miskala 06/01/2010
SEALD DIRECTOR	Laurie Burke 6/1/10
REVIEW COMPLETION DATE	06/01/2010
ESTABLISHED NAME	Ranibizumab injection
TRADE NAME	Lucentis
APPLICANT	Genentech
ENDPOINT(S) CONCEPT(S)	Near vision activities Distance vision activities
INSTRUMENT(S)	NEI-VFQ near vision activities and distance vision activities subscales
INDICATION	Treatment of macular edema following retinal vein occlusion
INTENDED POPULATION(S)	Patients with macular edema following retinal vein occlusion

A. EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Anti-Infective and Ophthalmology Products regarding BLA 125156/S053 for Lucentis (ranibizumab injection). The sponsor submitted an efficacy supplement to support an indication for the treatment of macular edema following retinal vein occlusion.

(b) (4)

B. SUGGESTED RESPONSES TO SPONSOR QUESTIONS

Not applicable.

C. STUDY ENDPOINT REVIEW

1 INSTRUMENT(S)

National Eye Institute Visual Functioning Questionnaire (NEI-VFQ)

The NEI-VFQ was developed with the intent to measure patient-reported visual functioning across a number of ophthalmological conditions (Mangione 1998, Mangione et al 2001). The following versions of the instrument exist:

- 51-item field test version of the NEI-VFQ (Mangione 1998)

- 25-item version of the NEI-VFQ (Mangione 2001); the NEI-VFQ25 includes an appendix of additional questions which can be incorporated into scale scoring to form the NEI-VFQ39.

The sponsor used the NEI-VFQ25 and the appendix of additional questions in their trials. The NEI-VFQ 25 items include a general health question and the other items form the following 11 subscales:

- General vision
- Near vision activities
- Distance vision activities
- Driving
- Peripheral vision
- Color vision
- Ocular pain
- Vision-related role difficulties
- Vision-related dependency
- Vision-related social functioning
- Vision-related mental health

The 25-item NEI-VFQ and the appendix item scoring are outlined in the following table:

Table 2. Scoring Key: Recoding of Items

Item Numbers	Change original response category [a]	To recoded value of:
1,3,4,15c[b]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a A3,A4,A5,A6,A7,A8,A9[c]	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25, A11a,A11b,A12,A13	1	0
	2	25
	3	50
	4	75
	5	100
A1,A2	0	0
	to	to
	10	100

[a] Precoded response choices as printed in the questionnaire.

[b] Item 15c has four-response levels, but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.

[c] "A" before the item number indicates that this item is an optional item from the Appendix. If optional items are used, the NEI-VFQ developers encourage users to use all items for a given sub-scale. This will greatly enhance the comparability of sub-scale scores across studies.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Source: http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf

The following table illustrates the NEI-VFQ scale scoring without and with the additional appendix items.

Table 3. Step 2: Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Table 4. Step 2: Averaging of Items to Generate VFQ-39 Sub-Scales (VFQ-25 + Optional Items)

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	2	1, A1
General Vision	2	2, A2
Ocular Pain	2	4, 19
Near Activities	6	5, 6, 7, A3, A4, A5
Distance Activities	6	8, 9, 14, A6, A7, A8
Vision Specific:		
Social Functioning	3	11, 13, A9
Mental Health	5	3, 21, 22, 25, A12
Role Difficulties	4	17, 18, A11a, A11b
Dependency	4	20, 23, 24, A13
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Source: http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf

Reviewer's comments: Sponsor included the additional appendix items into the near and distance activities scale scoring. The sponsor also reordered some of the original instrument items; thus, the item numbering of the additional appendix items does not reflect the sponsor's instrument item numbering. See near vision activities and distance vision activities item listing below that illustrates the item numbering changes that should be taken into consideration in item/scale scoring.

(b) (4)

(b) (4)

These two subscales consist of the following items:

Near vision activities subscale

- Item 5: Difficulty reading ordinary print in newspapers
- Item 6: Difficulty doing work or hobbies that require to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools

- Item 7: Difficulty finding something on a crowded shelf
- Item A3 (item 7A on sponsor's questionnaire): Wearing glasses, difficulty reading the small print in a telephone book, on a medicine bottle, or in legal forms
- Item A4 (item 7B on sponsor's questionnaire): Difficulty figuring out whether bills are accurate
- Item A5 (item 7C on sponsor's questionnaire): Difficulty doing things like shaving, styling your hair, or putting on makeup

Distance vision activities subscale:

- Item 8: Difficulty reading street signs or the names of stores
- Item 9: Difficulty going down steps, stairs, or curbs in dim light or at night
- Item 14: Difficulty going out to see movies, plays, or sports events?
- Item A6 (item 10A on sponsor's questionnaire): Difficulty recognizing people you know from across the room
- Item A7 (item 10B on sponsor's questionnaire): Difficulty taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)
- Item A8 (item 10C on sponsor's questionnaire): Difficulty seeing and enjoying programs on TV?

Reviewer's comment: Sponsor includes additional items from the NEI-VFQ appendix into the scale scoring. Sponsor reordered some of the original NEI-VFQ items. The instrument scoring outlined in the table above is specified based on the original instrument item numbering and needs to be modified for the sponsor's instrument. It is unclear why some of the distance activities items were grouped under question 10 which is measuring peripheral vision.

2 TARGETED LABELING CLAIMS

Sponsor is pursuing the following claims:

Indication:

For the treatment of patients with macular edema following retinal vein occlusion

(b) (4)

(b) (4)

Reviewer's comment: Whether it is appropriate to include the (b) (4) *will depend on the following:*

(b) (4)

It is questionable whether (b) (4) *t improvements are clinically relevant; see section "7. Interpretation of scores" and review summary at the end of this document for more information.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comments: (b) (4)

(b) (4)

3 ENDPOINT MODEL

BRAVO (FVF4165g): A phase III, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in subjects with macular edema secondary to branch retinal vein occlusion

Primary endpoint: mean change from baseline in BCVA score at 6 months

Key secondary endpoints:

- Proportion of subjects who gained ≥ 15 letters in BCVA score at month 6 compared to baseline
- Proportion of subjects with a central foveal thickness ≤ 250 μm at month 6
- Proportion of subjects who lost < 15 letters in BCVA score at month 6
- Mean change from baseline in BCVA score over time up to 6 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months
- Mean change from baseline in the NEI-VFQ-25 near activities subscale over time up to 6 months
- Mean change from baseline in the NEI-VFQ-25 distance activities subscale over time up to 6 months

CRUISE (FVF4166g): A phase III, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in subjects with macular edema secondary to central retinal vein occlusion

Primary endpoint: Mean change from baseline in BCVA score at 6 months

Key secondary endpoints:

- Proportion of subjects who gained ≥ 15 letters in BCVA score at month 6 compared with baseline
- Proportion of subjects who lost < 15 letters in BCVA score at month 6 compared with baseline
- Proportion of subjects with a central foveal thickness of ≤ 250 μm at month 6
- Mean change from baseline in BCVA score over time up to 6 months
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months
- Mean change from baseline in the NEI-VFQ25 near activities subscale over time up to 6 months
- Mean change from baseline in the NEI-VFQ25 distance activities subscale over time up to 6 months

Sponsor also submitted the following endpoint model:

Table 1: Proposed endpoint model for Genentech's Phase III trials (BRAVO and CRUISE)*†

Concept	Endpoint	Completion of assessment	Hierarchy of study endpoints
Improvement in vision (VA)	Mean change from baseline in BCVA score at 6 months	Clinician	Primary
	Proportion of patients who gain at least 15 letters in BCVA score at 6 months compared with baseline	Clinician	Secondary
	Mean change from baseline in BCVA score over time up to 6 months		
	Proportion of patients who lose fewer than 15 letters in BCVA score at 6 months		
Anatomical measures (foveal thickness)	Proportion of patients with a central foveal thickness of ≤250 µm, assessed on OCT, at 6 months	Clinician	Secondary
	Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months		
Improvement in patient perception of visual function	Mean change from baseline in the NEI VFQ-25 near vision subscale over time up to 6 months of follow-up	Patient (interviewer-administered)	Secondary
	Mean change from baseline in the NEI VFQ-25 distance vision subscale over time to 6 months of follow-up		
Improvement in reading speed	Mean change from baseline in the number of correctly read words per minute on the *reading speed assessment* over time to6 months of follow up	Clinician	Exploratory

(b) A full list of endpoints is included in Genentech's Phase III trials FVF4165g and FVF4166g [*Placeholder* for link].

†BCVA refers to BCVA in the study eye based on the ETDRS VA chart and assessed at a starting test distance of 4 meters. In addition, all other ocular efficacy outcome measures, such as those assessed on OCT and fluorescein angiography, refer to the study eye only.

4. CONCEPTUAL FRAMEWORK

Sponsor submitted the following conceptual framework:

Table 3: Conceptual framework for the near and distance vision activities subscales of the NEI-VFQ* and reading speed assessment

(b) (4)

Concept	Subscale	Items
Activities impacted by RVO	Near vision*	• difficulty reading ordinary print in newspapers (Q5) • difficulty doing work or hobbies that require you to see well (Q6) • difficulty finding something on a crowded shelf (Q7) • difficulty reading the small print in a telephone book, on a medicine bottle, or on legal forms (Q7a)† • difficulty figuring out whether bills you receive are accurate (Q7b)† • difficulty doing things like shaving, styling your hair, or putting on makeup (Q7c)†
	Distance vision*	• difficulty reading street signs or the names of stores (Q8) • difficulty going down steps, stairs, or curbs in dim light or at night (Q9) • difficulty going out to see movies, plays, or sports events (Q14) • difficulty recognizing people you know from across a room (Q10a)† • difficulty taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking) (Q10b)† • difficulty seeing and enjoying programs on TV (Q10c)†
Reading speed	Not applicable	• *description of reading speed assessment:* (Reading speed with use of enlarged text is assessed as an indicator of the patient's ability to use current vision to perform day-to-day tasks with the help of magnifiers or computer systems that magnify text.)

*Items assessed using a 5-point Likert-type severity response scale with 1=No difficulty to 4=Extreme difficulty, 5=Stopped doing this because of your eyesight, and 6=Stopped doing this for other reasons or not interested in doing this; no recall period specified.

†The version of the NEI VFQ-25 used in the Phase III clinical trials included six optional items from the questionnaire's supplemental appendix, which were added to the near and distance vision activities subscales These additional items were included to enhance the performance of pre-specified subscales.

5 CONTENT VALIDITY

The original development work by Mangione et al (1998) included 26 patient focus groups (a total of 246 subjects) with patients with primary open-angle glaucoma (n=82), diabetic retinopathy (n=58), age-related macular degeneration (n=35), cytomegalovirus retinitis (n=17), cataracts (n=42), and low vision from any cause (n=12).

Reviewer's comment: The original development work did not include patients with retinal vein occlusion.

Sponsor submitted the following table to illustrate the development work:

Table 2: Summary of available evidence regarding the validity of NEI VFQ-25

*Development of the NEI VFQ-51**
• Qualitative research (published in 1998) in patients with POAG (n=82), DR (n=58), AMD (n=35), CMV retinitis (n=17), cataracts (n=42), and low vision from any cause (n=12) • 26 Focus groups conducted to assess the influence of visual disability on individuals' HRQoL, including visual function, emotional well-being, and social functioning • Item generation based on patients' input (NEI VFQ-51)

*Development of the NEI VFQ-25**
• Quantitative research (published in 2001) in patients with age-related cataracts (n=135), AMD (n=143), DR (n=181), POAG (n=160), CMV retinitis (n=54), low vision from any cause (n=102), and low vision with no underlying disease (n=122) • Pooled datasets from pilot testing (n=246 patients) and psychometrics field test (n=598; convenience sample of n=96 returned to the practice to complete the NEI VFQ-51 a second time for test-retest assessment) • Item reduction (NEI VFQ-25) • Qualitative research in field test participants after administration of the NEI VFQ-51 • Exit cognitive debriefing testing interviews

Content validity of NEI VFQ-25 in RVO†
• Pilot qualitative research in 2007 in RVO population involving face-to-face in-depth interviews (n=15 patients) to document the comprehensiveness of the interview-administered NEI VFQ-25 • Qualitative research in 2009 in RVO population involving face-to-face in-depth interviews (n=19 patients) to document content validity of the interview-administered NEI VFQ-25 and appended items.

*Documentation of the psychometric properties of the NEI VFQ questionnaires in patients with visual problems**
• Psychometric properties documented primarily in patients with AMD as well as other ocular conditions (central RVO, glaucoma, cataract, and DR) • Other studies analyzed the relationship between the NEI VFQ-25 and clinical parameters (i.e., VA and depression) • Concurrent validity of two reading items from the NEI VFQ-25 with reading • As patients reported greater difficulty reading (higher response), reading speed decreased. Self reported reading measured by the VFQ reading items is directly correlated with measured reading speed.(41) • Supporting psychometric properties are described in detail in Table 4 and Table 5

Documentation of the psychometric properties of the NEI VFQ-25 in RVO†
• Ranibizumab clinical trials (BRAVO FVF4165g, CRUISE FVF4166g) as well as Phase II and Phase III randomized control trials from 2006 to 2009 in RVO populations • Concurrent validity of two reading items from the NEI VFQ-25 with reading speed

*Questionnaire is administered in patients with an ocular condition.

†Questionnaire is administered in patients with RVO.

As illustrated in the table above, the sponsor conducted qualitative research to support content validity of the NEI-VFQ in the retinal vein occlusion population.

- A pilot qualitative research in 2007 that included 15 in-depth face-to-face interviews in RVO patients with bilateral VA impairment
- Qualitative research in 2009 that included 19 in-depth face-to-face interviews in RVO patients with normal VA in the fellow eye

Reviewer's comments: The sponsor described the 2009 qualitative research in the submission. 2007 qualitative research was not included in the submission.

The sponsor's target population for 2009 qualitative research does not fully represent the clinical trial target population. The 2009 qualitative research included RVO subjects who have normal VA in the fellow eye; the patients enrolled in clinical trials did not all have a normal VA in the fellow eye. Although no patients with bilateral visual impairment were enrolled in the qualitative research, this may not be a major limitation considering that a relatively small number of patients with bilateral vision loss were enrolled in sponsor's phase 3 trials.

Sponsor states that the 2009 qualitative research included an open-ended concept elicitation phase and a cognitive debriefing interview.

Main inclusion criteria for the 2009 qualitative research:

- At least 18 years old
- Diagnosed with branch RVO or central RVO for 12 months or less
- VA of 20/25 to 20/640 (Snellen equivalent) in the RVO-affected eye with use of habitual correction or BCVA or uncorrected (not based on pinhole VA)
- Mean central subfield thickness $\geq$ 250μm on Stratus OCT in the RVO-affected eye
- Fluent in English and capable of participating in a 90-minute interview

More detailed criteria are outlined in section 3.2.2. of gn5742b-content-validation.doc.

Demographic characteristics of patients enrolled:
19 patients enrolled
11 men/8 women
Average age 51.5 years; range from 24.3 to 80.3 years
15 were white, 2 African American, 1 Asian, 1 unknown
3 with graduate degree, 1 college graduate, 8 some college, 5 completed high school
7 living with spouse/significant other, 5 living alone, 4 with significant other/spouse/children, 2 with children only, 1 living with relatives

VA in the affected eye: 20/30+1 to 20/400
VA in the fellow eye: 20/20 to 20/40-1

Reviewer's comments: It is unknown how many patients with branch RVO and how many patients with central RVO were enrolled. The content validity evidence is not presented by the type of RVO. The clinical division should think from the clinical perspective whether it is likely that patients with branch RVO and central RVO would present different issues with their condition or not. If not, then combining and presenting the findings overall is appropriate.

(b) (4)

The sponsor summarizes the 2009 qualitative research findings as follows (p.25-26 on GN6035A Evidence Dossier, v9 0):

- Reading ordinary print on paper (e.g., newspaper, book) n=16
- Reading small print (e.g., maps, bills, labels) n=9
- Reading electronic screen (e.g., email, reading captions on TV), irrespective of distance
- Self-care activities such as shaving n=3, brushing teeth or washing face n=2
- Other activities requiring minutia (e.g, sewing n=2, painting n=1, fishing n=1, embroidery n=1)
- See road markings n=2
- Directional or store signs n=10
- Driving
    - Drive during the day n=13
    - Drive at night n=10
    - Hazardous weather or other conditions n=4
- Writing n=1

Reviewer's comments: These findings suggest that near and distance reading/recognizing signs/markings type activities and driving are a concern in this patient population. The question now is whether the NEI-VFQ near and distance vision activities subscales adequately assess the concerns the patients have expressed. Driving appears an important concern for the subjects, but the sponsor did not include driving in their trials as a key endpoint.

Sponsor also summarizes their concept elicitation findings in the following tables separately for near activities and distance activities concepts.

Sponsor determined that concept saturation was achieved if

- A concept was elicited in more than one set of interviews
- If the concept was elicited only in the last interview, then the saturation was considered questionable; therefore, further data collection through additional interviews would have been recommended.

Sponsor also states the following:
"Saturation is different from a frequency count. The quantity of data in a concept is not theoretically important to the process of saturation, and richness of data derived from detailed description and not by the number of times a concept is saturated."

Reviewer's comment: This reviewer agrees with the sponsor's approach in general, although the number of patients that expressed each concept, the number of patients that have difficulty with each concept, and their sociodemographic/medical characteristics are useful in determining saturation.

Table 5. Saturation Grid for Near Vision Impact

Spontaneous Elicited Concepts Near Vision Impacts	Patient Interviews				Saturation (Frequency)
	1–4	1–4 vs. 5–9	1–9 vs. 10–15*	1–15 vs. 16–20	
Reading					
Ordinary print	3	3 vs. 4	7 vs. 4	11 vs. 5	**Yes** 16/19
Small print	2	2 vs. 4	6 vs. 2	8 vs. 1	**Yes** 9/19
Computer screen	2	2 vs. 3	5 vs. 0	5 vs. 1	**Yes** 6/19
Self-care (near vision)	1	1 vs. 1	2 vs. 0	2 vs. 2	**Yes** 4/19
Activities requesting close vision	1	1 vs.1	2 vs. 2	4 vs. 1	**Yes** 5/19
Identifying objects at close distance	1	1 vs. 0	1 vs. 0	1 vs. 0	**No** 1/19
Taking care of animals	0	0 vs. 0	0 vs. 1	1 vs. 0	**No** 1/19
Writing	1	1 vs. 0	1 vs. 0	1 vs. 0	**No** 1/19

* No patient number 13.

Table 10. Saturation Grid For Distance Vision Impact

Spontaneous elicited concepts distance vision impacts	Patient Interviews				Saturation (Frequency)
	1–4	1–4 vs. 5–9	1–9 vs. 10–15*	1–15 vs. 16–20	
Reading					
Reading ordinary print from a distance	4	4 vs. 3	7 vs. 2	9 vs. 2	**Yes** 11/19
Reading from a distance	0	0 vs. 3	3 vs. 1	4 vs. 2	**Yes** 6/19
Driving					
Driving during the day	4	4 vs. 4	8 vs. 4	12 vs. 1	**Yes** 13/19
Driving at night	3	3 vs. 3	6 vs. 4	10 vs. 0	**Yes** 10/19
Driving in bad conditions	1	1 vs. 3	4 vs. 0	4 vs. 0	**Yes** 4/19
Seeing people	0	0 vs. 3	3 vs. 1	4 vs. 0	**Yes** 4/19
Activities involving motion					
Patient is in motion	0	0 vs. 2	2 vs. 1	3 vs. 0	**Yes** 3/19
Sports (watching) object is in motion, patient is watching	0	0 vs. 2	2 vs. 0	2 vs. 0	**Yes** 2/19
Sport (playing) object and patient are in motion	0	0 vs. 1	1 vs. 0	1 vs. 1	**Yes** 2/19

* No patient number 13.

Sponsor then matches the concepts identified to the items on the NEI-VFQ near and distance activities subscales in the following table:

Table 30. Conceptual Framework

		Concept Spontaneously Elicited in Patients	NEI VFQ-25 Item
Activities that require near vision	→	Reading ordinary print (newspaper, book) small print (map, label) print on the computer (e-mails)*	Q5: Difficulty reading ordinary print in newspapers Q7a: Difficulty reading the small print in a telephone book, on a medicine bottle, or on legal forms Q7b: Difficulty figuring out whether bills you receive are accurate
	→	Shaving Brushing teeth, washing face	Q7c: Difficulty doing things like shaving, styling your hair, or putting on makeup
	→	Identifying objects*	Q7: Difficulty finding something on a crowded shelf
	→	Sewing Fishing (can't see hook) Embroidery	Q6: Difficulty doing work or hobbies that require you to see well up close
Activities that require distance vision	→	Driving Driving at night Driving in bad conditions	Independent subscale of the NEI VFQ-25 (items 15a, 15b, 15c, 16, 16a)
	→	Reading signs Reading small print (distance) (e.g., scoreboard, street sign, street name, TV caption)	Q8: Difficulty reading street signs or the names of stores Q10c: Difficulty seeing and enjoying programs on TV
	→	Sports (watching) (e.g., not seeing player, ball [baseball])	Q14: Difficulty going out to see movies, plays, or sports events
	→	Seeing people	Q10a: Difficulty recognizing people you know from across a room
	→	Activities involving motion (e.g., walking, jogging, biking) Sports (playing) (e.g., tennis, bowling, golf)	Q9: Difficulty going down steps, stairs, or curbs in dim light or at night Q10b: Difficulty taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)

*Concept is not assessed by the NEI VFW-25.
**Concept is not saturated; however, it is assessed in the NEI VFQ-25.

Sponsor summarized the results of the concept elicitation interviews as follows:

> "The results confirmed that the concepts assessed by the two scales are representative of the universe of content that describes the impact on activities experienced by patients with RVO. Saturated concepts categorized as near vision impacts included reading (e.g., ordinary print, small print, and print on the computer), self care, and activities requesting close vision (e.g., sewing, painting, fishing, embroidery).
> Five of the six items in the near vision subscale (Q5—reading ordinary print in newspapers; Q6—hobbies that require you to see well up close; Q7a—reading small print; Q7b—figuring out whether bills you receive are accurate; Q7c—shaving, styling your hair, or putting on makeup) matched these saturated concepts. One item in the near vision subscale (Q7—difficulty finding something on a crowded shelf) did not match the saturated concepts. Saturated concepts categorized as distance vision impacts included reading (e.g., signs, from a distance, small print from a distance), driving (e.g., during the day, at night, in bad conditions), seeing people, and activities involving motion (e.g., patient in motion, person [player] in motion); this list mirrors all of the six items distance vision subscale (Q8—reading street signs or the names of stores; Q9—going down steps, stairs or curbs in dim light or at night; Q10a—recognizing people you know from across

a room; Q10b—taking part in active sports; Q10c—seeing and enjoying programs on TV; Q14—going out to see movies, plays, or sports events).

Patients confirmed that reading was the most important issue. Patients also identified the sub-concept of reading on a computer screen as important. This concept is not currently captured in the near vision subscale of the NEI VFQ-25; however, reading on a computer depends on patients' interest in electronic devices and the availability of such device to patients 50 years and older. Because the questionnaire was developed during the 1990s, this concept might not have been considered at the time of development. This concept might be considered for inclusion in future new or revised measurement tools for visual functioning.

These findings are consistent with the findings from previous qualitative research with patients with central vision loss.7; 40 In the questionnaire development publication, the most frequently reported vision related limitations included reading ordinary print, driving during the daytime or in familiar environments, trouble seeing clearly, and driving at night.

In previous research conducted about AMD,41 writing has been identified as an important concept by patients; yet this concept is not included in the near vision subscale. However, it was not clear from the previous study report whether this new concept was spontaneously elicited or probed. In the questionnaire-development publication, writing was not reported as a concept elicited from patients. In the current research, only 1 patient of 19 spontaneously indicated that RVO affected his ability to write, because he sometimes did not distinguish the line or wrote over his own writing because of blurry vision. On the basis of these findings in this sample, we do not consider the concept of writing to be important for patients with confirmed RVO.

The patients interviewed in this additional qualitative research considered driving to be an activity impacted by the loss of distance vision. The concept of driving was considered by the developers of the NEI VFQ-25 and is captured as its own independent domain. Sex differences regarding driving and the relatively advanced age of RVO prevalence support this approach."

Reviewer's comments:

In general, this reviewer agrees with the sponsor's conclusions. The patient concept elicitation interviews suggest that near and distance reading activities are the core activities affected. Reading computer screen is not included in the NEI-VFQ, but the concept of reading is there. It is unclear to this reviewer whether conceptually it is a critical concept missing from the NEI-VFQ or not.

The NEI-VFQ item on difficulty finding something on a crowded shelf is included in the NEI-VFQ, but was not considered as a saturated concept based on the sponsor interviews, although

later in the cognitive interviews the subjects do acknowledge having issues with this activity suggesting that the item may not be irrelevant to the subjects.

Writing was mentioned spontaneously only by 1 out of 19 subjects; this evidence suggest that it may not be a critical concept missing from the instrument.

Driving also appears an important area of concern for the subjects in terms of frequency of reporting. Driving is a separate subscale on the NEI-VFQ, but the sponsor did not pursue driving as key endpoint. Therefore, content validity of that domain is not evaluated herein.

The NEI-VFQ does not specify a recall period for the assessments. Although many questions are asked in present tense, it is unclear what time-frame subjects are using when responding to questions about activities that may not occur on a daily basis (e.g., going out to see movies, plays, or sports events). And if they have not done the specified activity recently, but still interested in doing it, it is not clear whether the subjects are answering these questions based on what they actually do or what they think they might be able to do.

In summary, the concept elicitation interviews suggest that the NEI-VFQ near vision and distance vision activity subscales seem to include items that are relevant to subjects with RVO.

Cognitive debriefing results:

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase

Concept elicitation			NEI VFQ-25 Item	Cognitive debriefing testing
CE Spontaneous Concepts	**Frequency of Concepts**	**Saturation (Yes/No)**		
Near vision impacts				
Reading ordinary print *e.g. newspaper, recipes*	n=15	Yes	• difficulty reading ordinary print in newspapers (Q5)	Q5 • 12 patients described the question to be asking whether they have trouble reading the newspaper in general • 5 patients interpreted the question to be asking about the ability to read the small font size of the newspaper • Other patients interpreted the question to be asking if they have their glasses (n=1) or if they read (n=1).
Reading small print *e.g. label, , medicine bottle, phone book, map*	n=9	Yes	• difficulty reading the small print in a telephone book, on a medicine bottle, or on legal forms (Q7a)	Q 7a • 9 patients understood the question as to be asking about difficulty with the small font size that is found in a telephone book, on a medicine bottle, or on legal forms • 2 patients interpreted the question as how well you can see up close • 3 patients understood the question as needing to wear glasses to read the small print. • 1 patient interpreted the question as having to do with your lifestyle and stated, "if you want to just give up and say, I'm blind, give up. But if you don't, then you do what you got to do, like bringing it closer to you, if you never wore glasses, admit you need glasses or contacts or whatever to do your daily lifestyle". • Other patients (n=4) understood the question in a variety of ways.
Reading (on computer screen)	n=6	Yes		

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase

Concept elicitation			NEI VFQ-25 item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
Shaving Brushing teeth, wash face, shower	n=3 n=2	Yes	• difficulty doing things like shaving, styling your hair, or putting on makeup (Q7c)†	Q 7c • 8 subjects understood that question to be asking whether they have difficulties performing everyday activities (i.e. missing spots shaving, cutting self shaving) • 6 patients interpreted the question to be asking whether or not they can see well enough (i.e. to put on makeup, recognize self in mirror) • 3 patients understood this question to be asking whether their vision problems made a difference in their appearance (i.e. makeup all over face, bad hairdo, shaved head) • Other patients understood the question to be asking whether everything is blurry (n=1) and if looking in a mirror is more difficult than looking at a newspaper (n=1).
Sewing 'Copy cat' painting Embroidery Fishing (can't see hook) Use of tools	n=2 n=1 n=1 n=1 n=1	Yes	• difficulty doing work or hobbies that require you to see well up (Q6)	Q 6 • 9 patients understood this question to be asking whether they can perform their chores and everyday activities without a problem • 4 patients understood this question to be asking if they can see well while performing these activities • 3 patients interpreted the question to be asking specifically about activities that require seeing welling up close. • Other patients interpreted the question to be asking whether they need to focus more (n=1) or if they have more difficulty now than they did before (n=1). One subject also mentioned that they thought the question itself was too vague and not specific enough.

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase

Concept elicitation			NEI VFQ-25 item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
Identifying objects	n=1	No	• difficulty finding something on a crowded shelf (Q7)	Q 7 • 6 patients understood this question to be asking about whether you can see what's on your shelf (i.e. is it hard to find things, can't see well enough to distinguish) • 6 patients interpreted the question to be asking whether or not they can pick the right item off the shelf (i.e. distinguish between different cans, difficulty finding things) • 2 patients understood the question to be asking if they need to look closer at items to recognize them and another two patients thought the question was well stated. • Others understood the question to be asking how quick they can see the item (n=1), if they can read labels (n=1), or if they can see the price on items at the grocery store (n=1).
Taking care of animals	n=1	No		
Writing	n=1	No		

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase				
Concept elicitation			NEI VFQ-25 Item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
			• difficulty figuring out whether bills are accurate (Q7b)	Q 7b • 13 patients understood the question to be asking about the difficulty determining whether a bill was accurate or reviewing/checking bills for mistakes (i.e., difficult adding numbers, multiplying). • 8 patients also understood the question to be asking about whether patients can see well enough to read bills (i.e., see numbers, text). • Other interpretations of the question included, ability to see well close (n=1), being able to distinguish at the bill in detail (n=1), whether can review a billthe bill can be reviewed without assistance (n=1), if a patient is paying their bill (n=1), and concentration (n=1).
Distance vision impacts				
Driving during day	n=13	Yes	• difficulty driving during the daytime in familiar places (15c)	
Driving at night	n=10	Yes	• difficulty driving at night (16)	
Driving in bad conditions	n=4	Yes	• difficulty driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic (16a)	

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase				
Concept elicitation			NEI VFQ-25 Item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
Reading signs Reading from a distance	n=10 n=7	Yes	• difficulty reading street signs or the names of stores (Q8)	Q 8 • 9 patients understood the question to be asking about distance vision (i.e., need to get closer to read signs and the ability to read a sign depends on how close or far a person is from the sign) • 8 patients understood the question to be asking about reading signs while driving • Other patients interpreted the question as asking about large print (n=1), outside/street vision versus inside vision (n=1), paying attention (n=1), and how lighting (daytime versus nighttime) and weather affect the ability to read a sign (n=1).
Reading small print from a distance *e.g., scoreboard, street sign, street name, TV caption*	n=5	Yes	• difficulty seeing and enjoying programs on TV (Q10c)†	Q 10c • 8 patients understood the question to be asking about whether a patient can see or watch the television without problems/straining such as distinguishing characters. • 3 patients understood the question as asking about the enjoyment of the television program. • Patients also referred to difficulty watching a specific type of program (e.g., sports) (n=2), difficulty seeing a ticker or caption (n=2), watching the same programs as before vision problems (n=1), tiredness of eyes (n=1), satisfaction with life and sight (n=1), and the glare on the television (n=1). • 3 patients also reported that the size and the distance (n=1) from the television would affect seeing and enjoying programs (on TV.

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase				
Concept elicitation			NEI VFQ-25 Item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
Activities involving motion (patient is seeing motion) *e.g. Not seeing player, ball (baseball)*	n=4	Yes	• difficulty going out to see movies, plays, or sports events (Q14)	Q 14 • 6 patients understood the question to be asking about the ability of patients to enjoy activities/lifestyle and be social/active. • 7 patients specifically considered difficulty watching sports events, while 5 considered watching movies (three of those subjects considered both sports events and movies). One patient also considered watching plays. • Other interpretations of the question included, being able to know what is going on (or depending on others to be informants) (n=4), how much effect vision has on the ability to see objects/screen (n=2), seeing far places (n=1), and distance vision at night (n=1). • Two patients reported that the different lighting in a movie theatre and sports event would impact the ability to see clearly (one of the two patients specifically stated that sports events are more lighted and therefore more vivid). • One patient also commented that large movie screens are different than sports events where a person would need to follow a moving ball.

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase				
Concept elicitation			NEI VFQ-25 Item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
Seeing people	n=3	Yes	• difficulty recognizing people you know from across a room (Q10a)†	Q 10a • 10 patients understood the question to be asking about being able to see people clearly across the room • 6 patients understood the questions to be asking about recognizing or distinguishing a person across the room • Other patients specifically interpreted the question as asking about seeing someone you know (e.g., husband, friends, relatives) across the room (n=4), social life (n=1), being able to see facial expressions (n=1), and being aware of surroundings (n=1). • Patients also interpreted the distance a person would be across a room in various ways: house party, church, sports game, 20 to 30 feet away, and 60 to 70 feet away. Two patients stated that they would have more difficulty depending on the size of a room (e.g., church or sports game versus a house party).

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase				
Concept elicitation			NEI VFQ-25 Item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
Patient is in motion *e.g. Walking, jogging, biking*	n=3	Yes	• difficulty taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking) (Q10b)†	Q 10b • Patients understood the question to be asking about the impact on various sports and activities. Specifically some patients considered golf (n=5), three patients reported not being able to see the golf ball after it was hit. • 5 patients interpreted the question to be asking about physical activity or movement, while others understood the question to be asking about social activities and personal hobbies (n=4). • 3 patients interpreted the question to be asking about difficulty with sports in general. 3 patients considered bowling in their interpretation of the question; one of the three understood difficulty with this activity to mean bluminess while bowling. • Other patients understood the question to be asking about limiting/giving up outdoor activities (n=2), everyday life/lifestyle (n=2), walking (n=1), football (n=1), baseball (n=1), throwing a ball in a hoop (n=1), coordination (n=1), and activities in general (n=1).
Sports (Watching) Object is in motion, patient is watching (n=2) *e.g., Not seeing player, ball (baseball)*	n=2	Yes	• difficulty seeing and enjoying programs on TV (Q10c)†	
Sports (Watching) Object is in motion, patient is watching *e.g., Tennis, bowling, golf*	n=2	Yes	• difficulty taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking) (Q10b)†	
Watching TV/computer screen	n=2	Yes	• difficulty seeing and enjoying programs on TV (Q10c)†	

Table 1: Summary table of spontaneous concepts mentioned during the concept elicitation phase				
Concept elicitation			NEI VFQ-25 Item	Cognitive debriefing testing
CE Spontaneous Concepts	Frequency of Concepts	Saturation (Yes/No)		
Hunting	n=2	No		
Photography	n=1	No		
			• difficulty going down steps, stairs, or curbs in dim light or at night (Q9)	Q 9 • 8 patients understood the question to be asking about how low lighting affected their ability to walk down stairs or curbs. • 5 patients also understood the question to be asking about safety and injury when walking down stairs or curbs in dim light or at night. • Other patients interpreted the question as asking about being more careful (n=4), depth or height perception (n=3), difficulty walking (n=2), coordination or balance (n=2), ability to walk down stairs independently (n=1), comfort/confidence going down stairs (n=1), and proper judgment (i.e., making a decision to do something within a person's abilities) (n=1). • 1 patient reported that while stairs would be difficult to navigate in dim light or at night, curbs would not be. • 5 patients only reported considering going down stairs in their interpretation of the question.

†: Item from the appendix

Sponsor concluded the following based on the cognitive debriefing:

> "Cognitive debriefing testing of the questionnaire revealed that the NEI VFQ-25 was easy to understand (n = 17) and easy to answer (n = 18). Most patients (n = 15) reported that they had no difficulty answering the questionnaire and that the response options were detailed enough.
>
> Because suggestions for modifying the questionnaire were provided by only a small subset of patients, it is not recommended to change any of the items in the questionnaire.
>
> A small number of patients provided suggestions to improve some of the items in the near and distance vision subscales. For instance, two patients suggested changing question 7 (finding something on a crowded shelf) and question 10 (noticing objects off to the side while walking along) by making these questions more specific. One patient indicated that the examples in question 10b (taking part in active sports or other outdoor activities that you enjoy [like golf, bowling, jogging, or walking]) and question 7a (reading the small print in a telephone book, on a medicine bottle, or on legal forms) were confusing. Two patients also did not understand question 10 (noticing objects off to the side while walking along), and one suggested deleting it. One patient did not understand question 10a (recognizing people you know from across a room), and another reported that it was unclear."

Reviewer's comments: In general, this reviewer agrees with the sponsor's conclusion with the exception of the following:

Concerns with interpretation of some of the near activities subscale items/response options:

Item on difficulty reading ordinary print in newspapers: Subjects considered newspapers, but also reading in general, e.g. magazines or books. The question seems to capture a broader concept of reading and not limited to reading newspapers.

Item on difficulty finding something on a crowded shelf: two patients did not understand the question and interpreted it to ask about searching in the wrong place or not remembering where the object was placed. Also, selecting a response option was sometimes related to the neatness/organization of the shelf rather than to visual impairment (e.g., 2 patients selected "little difficulty" because the shelf was not neat/organized, 1 patient selected "no difficulty at all" because her shelves were organized.

Item on difficulty doing things like shaving, styling your hair, or putting on makeup: Sponsor states that 5 patients selected "no difficulty at all" because they do not wear makeup and do not think about shaving (n=1), do not do hair (n=1), and use an electric shaver (n=1) (note: these numbers do no add to 5 in the sponsor submission). This is of a concern that no difficulty response option was selected when the subject should have chosen "stopped doing this for other reasons or not interested in doing this". The question is whether this misclassification creates a problem with the scale scoring. No difficulty on this item is scored as "100" and stopped doing

this for other reasons or not interested in doing this is scored as missing. It is this reviewer's opinion that the misclassified item score of 100 may raise the average subscale score; if the misclassification occurred at baseline then it would be more difficult for the sponsor to demonstrate improvement in the scale. This may be more problematic for the FDA if the misclassification occurred at follow-up only. The FDA statistician should look for inconsistencies in the baseline and follow-up scores.

Concerns with interpretation of some of the distance activities subscale items/response options:

Item on difficulty going down steps, stairs, or curbs in dim light or at night: One patient selected the response option no difficulty at all because "people walking in front of the person indicated whether steps or curbs were ahead". This is just one patient, but again suggests variability how to interpret "no difficulty at all" response option.

Item on difficulty taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking): One patient commented on the inconsistency in the question; bowling is not an outdoor activity. One patient did not understand the question and interpreted it to ask about watching someone to play sports. Although small number of patients commented on the issues, both seem valid concerns.

Difficulty seeing and enjoying programs on tv; 3 of 19 subjects understood the question to ask about the enjoyment of the tv program, 3 of 19 subjects noted that size and distance from tv would affect seeing and enjoying programs. Enjoyment is a concept different from the activity of seeing tv programs and really should not have been included in the item. However, only a small number of patients considered enjoyment when responding the question. One subject chose "no difficulty at all" when they moved closer to the television if they could not see; however, another subject "moderate difficulty" because needed to sit closer to the television to see clearly. So, there is some evidence to suggest that some patients are unclear whether to rate the activity before or after any accommodation. The effect of screen size to be able to see tv was also mentioned.

Difficulty going out to see movies, plays, or sports events: One patient commented that only blind person would "not be able to see those things"; another person reported that the question is not clear because of different scenarios (e.g., large movie screen vs concentrating on a moving ball at a sports event).

In summary, these cognitive debriefing interviews suggested that there is some variability what "no difficulty at all" response option means to the subjects. The concept of "enjoyment" is problematic in the question difficulty seeing and enjoying programs on tv. A few patients related finding something on a crowded shelf to neatness/organization and not to visual issues. Some patients expanded the questions to capture similar activities (e.g., difficulty reading ordinary print in newspapers was interpreted to include reading in general including magazines or books).

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Sponsor submitted the following tables to summarize the work in the literature related to NEI-VFQ's psychometric properties.

Table 4: Summary of Evidence of Psychometric Properties of the NEI VFQ-25 or NEI VFQ-51

					Psychometric Properties				
	Instrument	Population (n)	Study Design	PRO Instrument(s)	Ct. V	Con. V	TRT	Res	MID
Berdeaux et al. 2005(7)	NEI VFQ-25 + 14 items*	AMD (114)	RCT		✓	✓		✓	
Cahill et al. 2005(43)	NEI VFQ-25	AMD (50)	RCT	SF-12					✓
Clemons et al. 2003(21)	NEI VFQ-25 + 14 items	AMD (4077)	Prospective Cohort Age-Related Eye Disease Study (AREDS)		✓	✓			
Cole et al. 2000(52)	NEI VFQ-51	Optic neuritis (244)	RCT Optic Neuritis Treatment Trial		✓	✓			
Deramo et al. 2003(13)	NEI VFQ-25*	Central RVO (51)	Observational			✓			
Dong et al. 2004(8)	NEI VFQ-25 + 14 items*	AMD (789)	RCT Submacular surgery trials	SF-36, Hospital Anxiety and Depression Scale (HADS), SST-VPVS		✓			
Fuhs et al. 2005(44)	NEI VFQ-25 + 14 items	AMD (974)	Prospective Cohort MARS			✓			
Globe et al. 2003(53)	NEI VFQ-25	Ocular disease (1917)	Prospective Cohort Los Angeles Latino Eye Study		✓				
Miskala et al. 2004(46)	NEI VFQ-25 + 14 items*	AMD (125)	RCT Submacular surgery trials	SF-36, HADS		✓			
Klein et al. 2001(48)	NEI VFQ-25	Diabetes neuropathy	Wisconsin Epidemiologic Study			✓			
Leys et al. 2008(45)	NEI VFQ-25*	AMD (1208)	RCT VISION					✓	

Table 4: Summary of Evidence of Psychometric Properties of the NEI VFQ-25 or NEI VFQ-51

	Instrument	Population (n)	Study Design	PRO instrument(s)	Psychometric Properties				
					Ct. V	Con. V	TRT	Res	MID
Lindblad and Clemons 2005(9)	NEI VFQ-25 + 12 items	AMD (4119)	Prospective cohort			✓		✓	✓
Maguire 2004(56)	NEI VFQ-25 + 12 items	AMD (1052)	RCT laser treatment		✓	✓			
Mangione et al. 1998(38)	NEI VFQ 51	AMD (108); cataract (93); DR (123), POAG (78), CMVR (37), low vision (90)	Prospective cohort	VF-14, ADVS, SF-36	✓	✓	✓		
Mangione et al 2001(39)	NEI VFQ-25	AMD (164); cataract (174); DR (181), POAG (149), CMVR (58), low vision (90)	Two observational studies		✓	✓			
Miskala et al. 2003(10)	NEI VFQ-25 + 12 items*	AMD (218)	RCT Submacular Surgery Trials	SF-36				✓	✓
Nichols et al. 2002(51)	NEI VFQ-25	Dry eye (75)	Prospective observational		✓		✓		
Paz et al. 2003(54)	NEI VFQ-25 (English, Spanish)	Population-based study (1916)	Los Angeles Latino Eye Study	SF-12		✓			
Suñer et al. 2009(3)	NEI VFQ-25*	AMD (716, 423)	RCT MARINA, ANCHOR	SF-36, VAS (General health)				✓	✓
Genentech unpublished study results (psychometric analysis report)(2,55)	NEI VFQ-25*	AMD (716, 423)	RCT MARINA, ANCHOR	SF-36 VAS (General health)	✓	✓			

Ct V: construct validity; Con V. concurrent validity; TRT: test-retest reliability; Res: responsiveness. MID: minimal important difference. RCT: randomized controlled trials.

*Interviewer administered questionnaire.

Documentation of the psychometric properties of the NEI VFQ-25 in RVO†
• Ranibizumab clinical trials (BRAVO FVF4165g, CRUISE FVF4166g) as well as Phase II and Phase III randomized control trials from 2006 to 2009 in RVO populations • Concurrent validity of two reading items from the NEI VFQ-25 with reading speed

*Questionnaire is administered in patients with an ocular condition.

†Questionnaire is administered in patients with RVO.

Reviewer's comments: Sponsor implies in the table above that no specific psychometric validation studies have been conducted in the RVO population. However, the work by Deramo et al (2003) and Awdeh et al (2010) evaluated some psychometric properties of the NEI-VFQ in the central retinal vein occlusion and branch retinal vein occlusion populations, respectively. More extensive psychometric validation has been conducted by the original instrument developer Mangione et al (1998) in several other ophthalmological conditions.

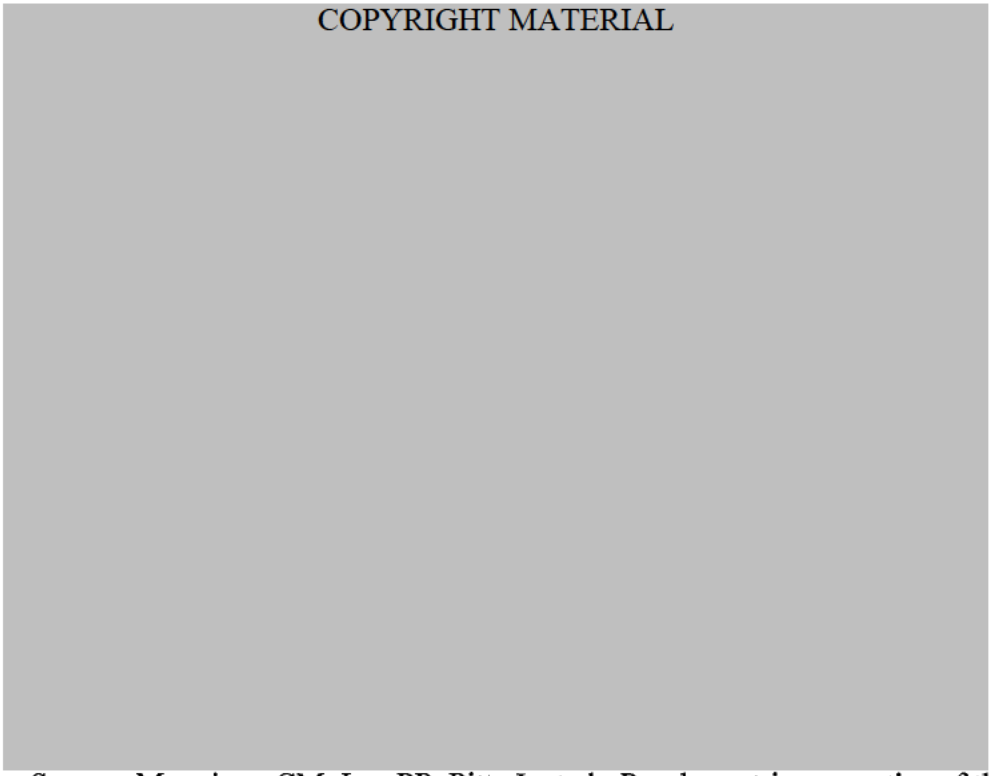
The following tables outline psychometric validation findings based on work by Mangione et al (1998) on the NEI-VFQ 51-item field version.

Psychometric validation of the 51-item NEI-VFQ field version

Paper by Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Arch Ophthalmol 1998; 116: 1496-1504.

Mangione et al (1998) evaluated measurement properties of the 51-item field test version of the NEI-VFQ across several eye conditions (diabetic retinopathy (n=123), ARMD (n=108), glaucoma (n=78), cataract (n=93), CMV retinitis (n=37), low vision (n=90)) and a reference group (n=122).

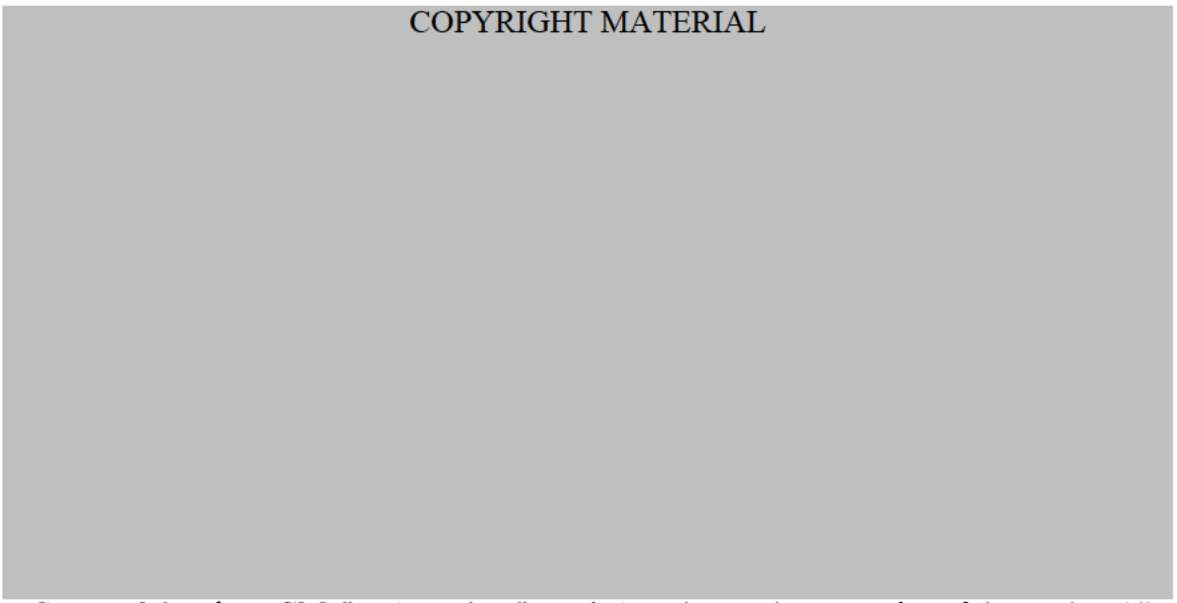
The following table outlines internal consistency and test-retest reliability findings.



Source: Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Arch Ophthalmol 1998; 116: 1496-1504.

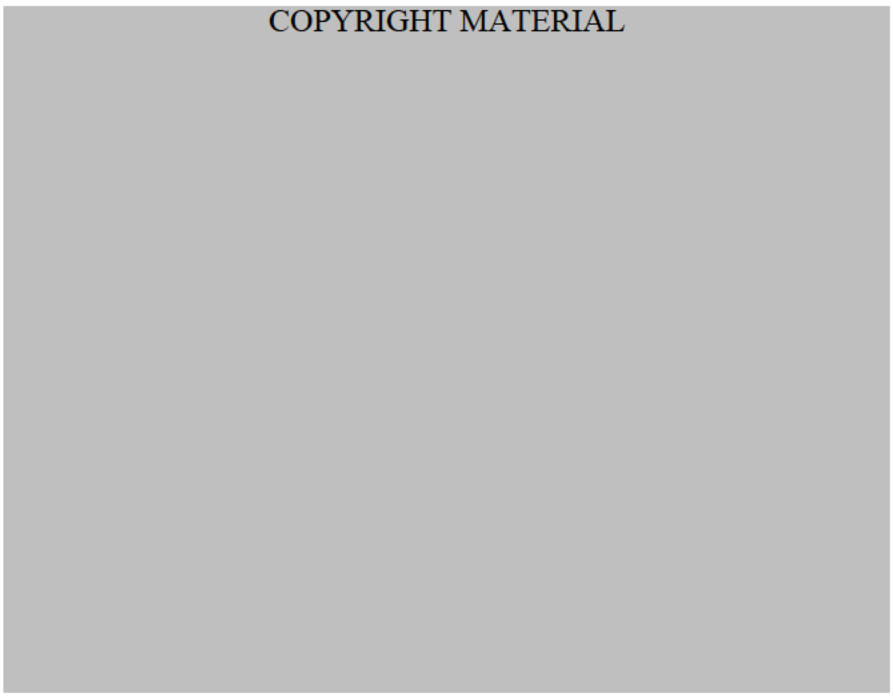
Reviewer's comments: Internal consistency and test-retest reliability for the near vision and distance vision subscales are adequate. Again these findings are based on a group of patients with other ophthalmological conditions, not RVO patients. Preferably, evidence of psychometric validity in the RVO population would be needed, but it is reassuring that no previous evidence exist that psychometric properties of the instrument vary by ophthalmological condition based on Mangione's research.

Mangione et al (1998) original research also provided evidence for construct validity as illustrated in the following table:



Source: Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Arch Ophthalmol 1998; 116: 1496-1504.

Reviewer's comments: The work by Mangione et al (1998) provided evidence for NEI-VFQ's construct validity. The NEI-VFQ activity-oriented scales (near, distance and driving) are more correlated with other scales assessing vision-targeted functioning than with scales that assess general health status (SF-36 PCS and MCS).



Source: Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Arch Ophthalmol 1998; 116: 1496-1504.

Reviewer's comments: Mangione et al (1998) work also suggests that current vision in the better- and worse-seeing eyes have the highest correlation with near vision and distance vision activities subscales. This provides further evidence for construct validity of these scales. See "interpretation" section of this review how better eye and worse eye changes are related to changes in the NEI-VFQ.

Source: Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Arch Ophthalmol 1998; 116: 1496-1504.

Reviewer's comments: Interscale correlations (Mangione et al 1998) provide evidence that there are several dimensions of vision-related functioning and higher correlation between near vision and distance vision scales suggest a more closely related activity related dimension. This was also evidenced in the earlier table by higher correlation with near and distance vision activities subscales with visual acuity.

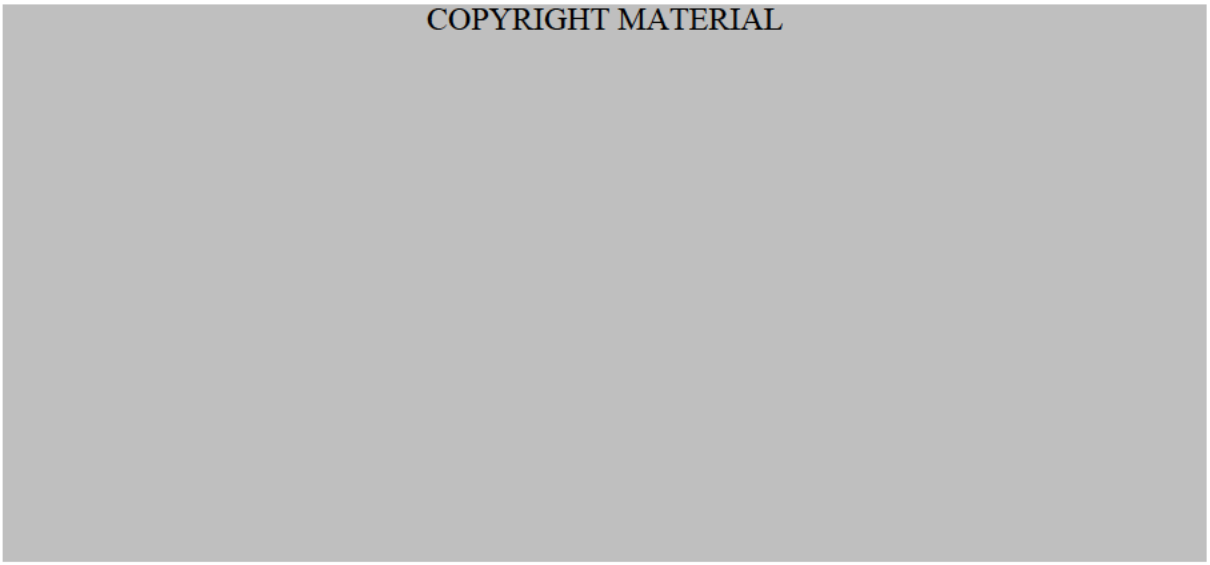
Psychometric validation of the NEI-VFQ 25

Paper by Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001; 119: 1050-1058.

The previous tables illustrated psychometric validity of the NEI-VFQ 51-item field version; the following tables illustrate psychometric validity of the NEI-VFQ-25. Two separate samples were included in the analysis: 262 persons who participated in the 1994 pilot test of the NEI-VFQ and 597 persons from the 1996 NEI-VFQ psychometric field test. These two datasets were combined and a total of 859 persons contributed data to these analyses.

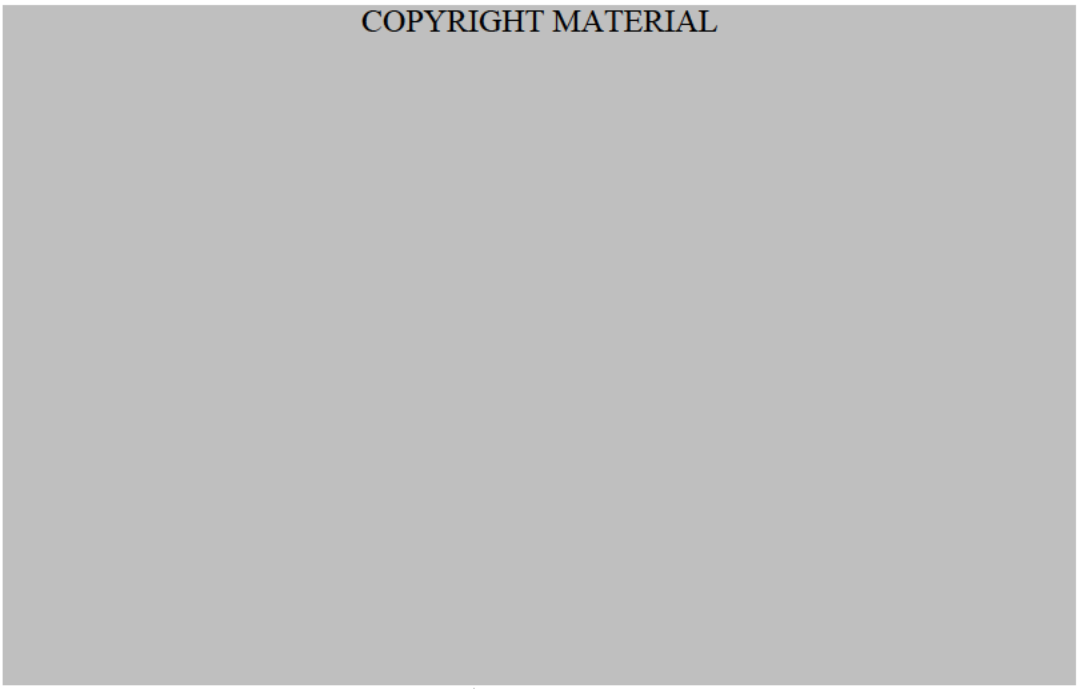
Again this work did not include patients with retinal vein occlusion.

The following figure shows evidence of between group validity of the NEI-VFQ25.



"Figure 1. Comparison of low-vision (n = 90) and cataract (n = 93) patients with reference patients (n = 122) on mean 25-item version of the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) subscale scores (field test sample only). Linear regression results for 2-group comparisons with the reference group, adjusted for age, sex, race, and medical comorbidities. The comparison of the low-vision group with the reference group on the driving subscale is not included because of a sample size of 12 for the low-vision group. Also, the sample size for the cataract group for the driving scale is 68. Asterisk indicates that all comparisons with the reference group were statistically significant at P<.001, except for general health and cataract (P<.04), general health and low vision (P<.03), and peripheral vision and cataract (P<.002); error bars, SEM."

Source: Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001; 119: 1050-1058.



Source: Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001; 119: 1050-1058.

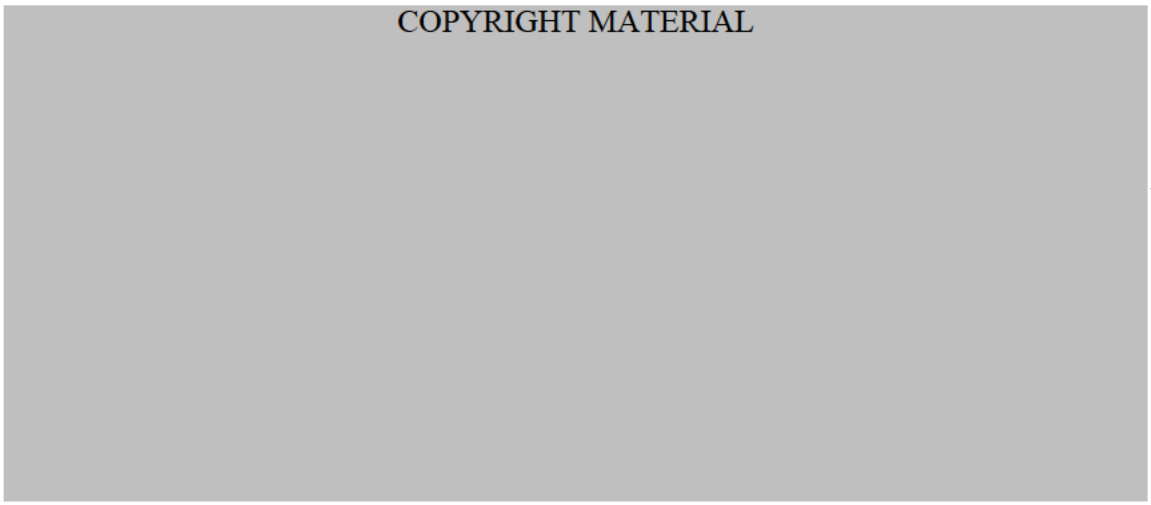
Reviewer's comments: Correlation of 3-item NEI-VFQ near and distance vision subscale scores with visual acuity is similar in magnitude as the correlation of the field version of these NEI-VFQ scales with visual acuity. However, it is noted here that the sponsor is including the NEI-VFQ25 appendix of additional questions into the instrument scoring. Thus, the sponsor will have 6 items in the near activities subscale and 6 items in the distance activities subscale.

Limited psychometric evidence from the RVO population

a) Patients with central retinal vein occlusion

Paper by Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2003; 121: 1297-1302.

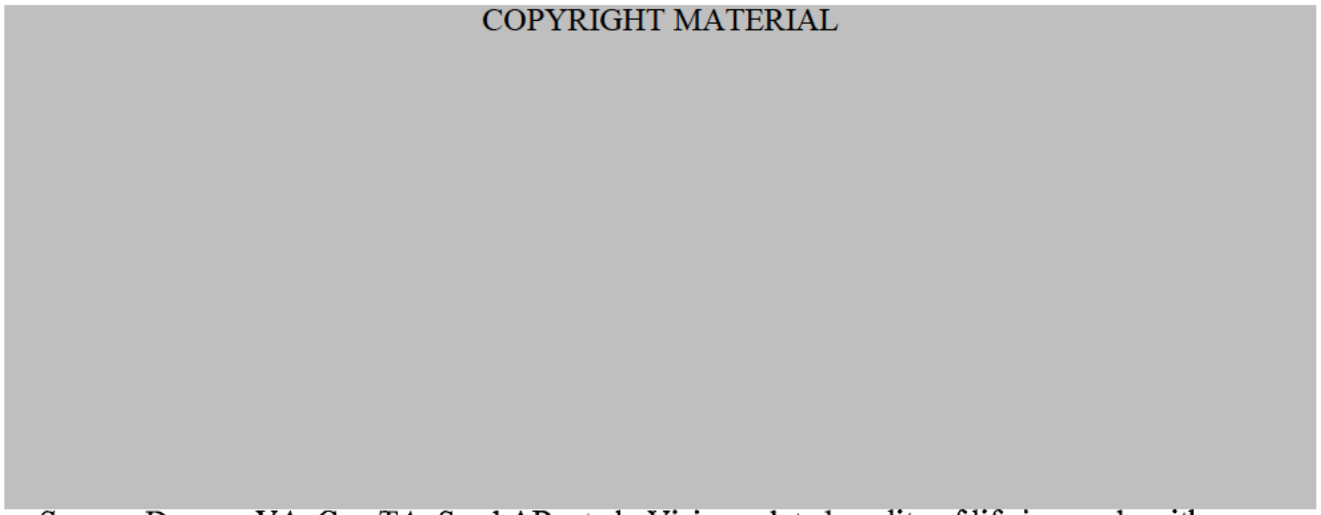
Deramo et al (2003) studies 51 patients with central retinal vein occlusion and interviewed these patients using the 25-item version of the NEI-VFQ without the appendix of additional questions. Mean age ± SD was 69.5 ± 13.1 years; 5 of 51 patients had bilateral central retinal vein occlusion; 53% were women, median VA in the affected eye was count fingers.



Source: Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2003; 121: 1297-1302.

Reviewer's comments: Overall, the CVO patients enrolled had moderate to little difficulty with near and distance vision activities. The near and distance vision scores were worse for CVO patients than the reference group, but similar to patients with diabetic retinopathy.

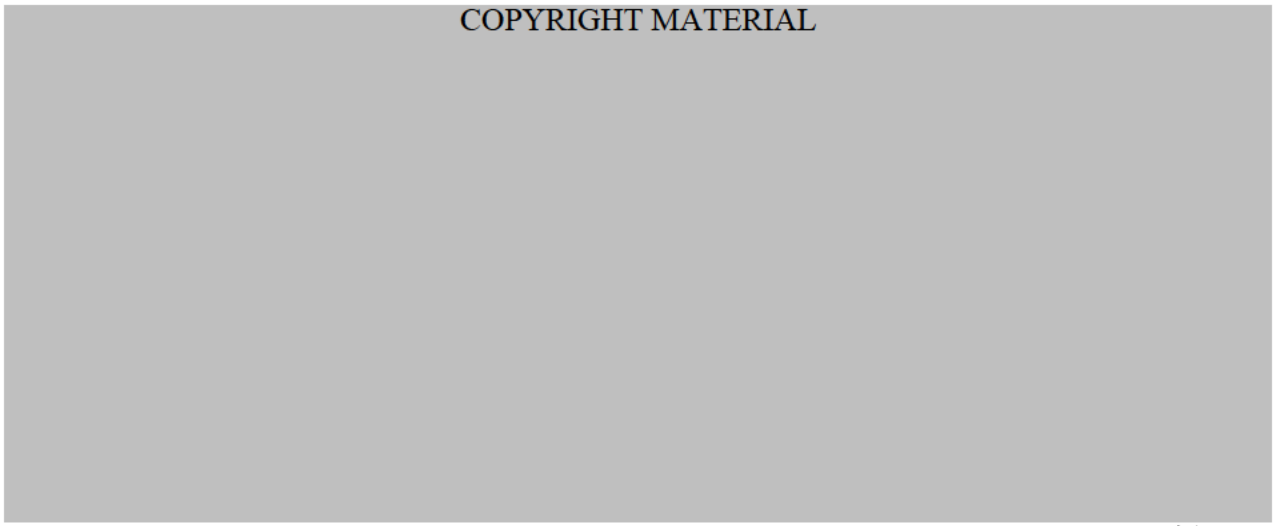
COPYRIGHT MATERIAL



Source: Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2003; 121: 1297-1302.

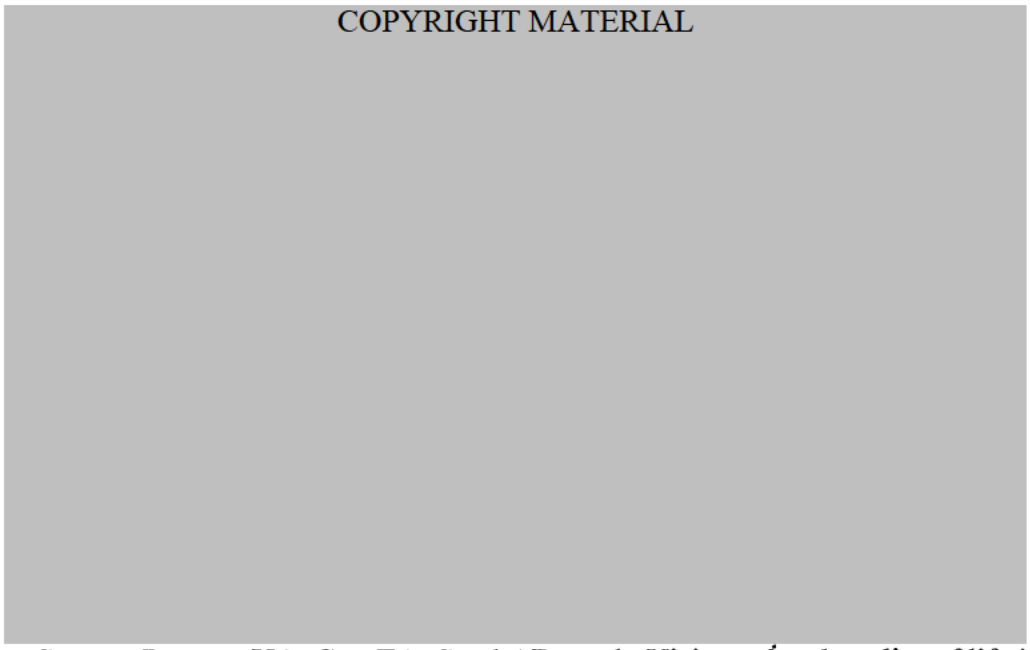
Reviewer's comments: The table above suggests that the NEI-VFQ near and distance vision subscale scores are more correlated with vision in the better-seeing eye than with vision in the worse-seeing eye in patients with central retinal vein occlusion.

COPYRIGHT MATERIAL



Source: Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2003; 121: 1297-1302.

Reviewer's comments: The authors performed additional analyses in patients with unilateral CVO and excellent visual acuity in the fellow eye (20/25 or better) and observed that these patients still demonstrated decreased vision-related quality of life as compared to reference group. So even if NEI-VFQ scores are more correlated with visual acuity in the better-seeing eye, the instrument seems to still capture vision-related decrement due to unilateral CVO when the vision in the better-seeing eye is good.



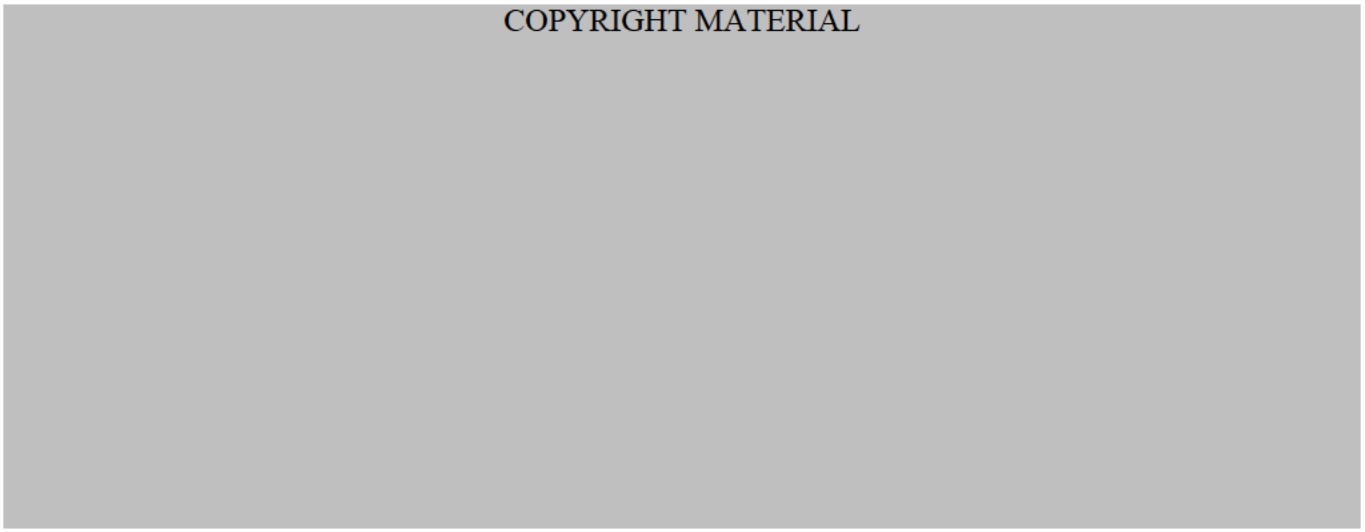
Source: Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2003; 121: 1297-1302.

Reviewer's comments: The table above shows evidence for construct validity of the near and distance vision subscales. The table also suggests that after controlling for general health, the correlation of better eye visual acuity with the near and distance activities vision subscales is stronger than without adjustment (see table 4 above). This also suggests that adjustment for general health status is important when interpreting NEI-VFQ scores.

b) Patients with branch retinal vein occlusion

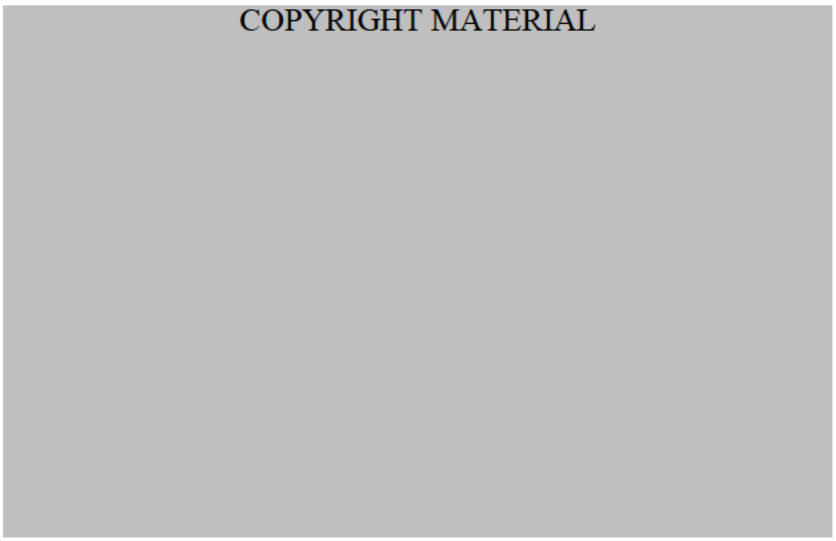
Paper by Awdeh RM, Elsing SH, Deramo VA, et al. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Br J Ophthalmol 2010; 94: 319-323.

Awdeh et al (2010) interviewed 46 patients with branch retinal vein occlusion. Patients were on average 67.8 ± 7.9 (SD) years old; 50% were women; visual acuity in the affected eye was a median of 20/60.



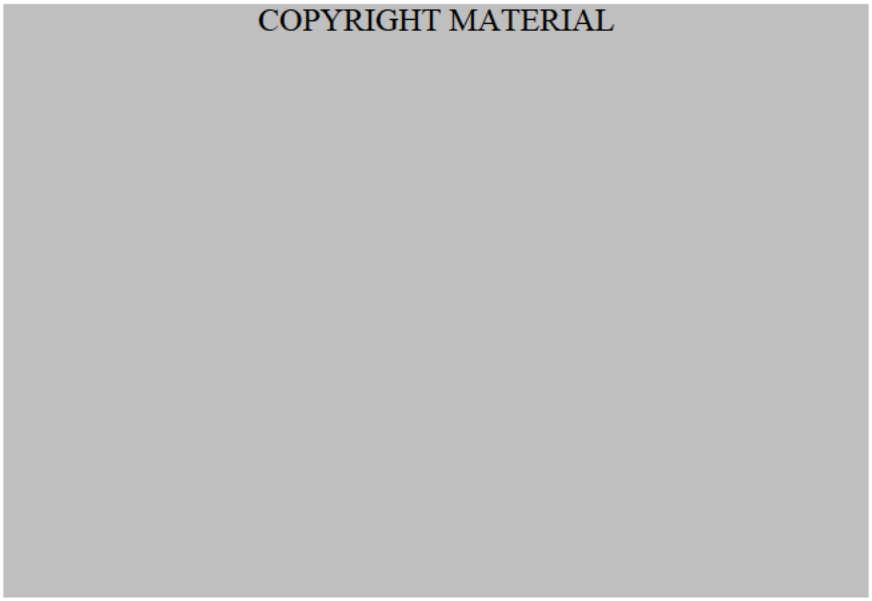
Source: Awdeh RM, Elsing SH, Deramo VA, et al. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Br J Ophthalmol 2010; 94: 319-323.

Reviewer's comments:
The table above suggests that patients with BRVO have a little difficulty with near vision and distance vision activities as compared to patients with CRVO who have little to moderate difficulty. These findings are consistent with what one would expect. The table also shows evidence for between-group validity.



Source: Awdeh RM, Elsing SH, Deramo VA, et al. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Br J Ophthalmol 2010; 94: 319-323.

Reviewer's comment: Scores in table 5 indicate that patients with unilateral branch retinal vein occlusion and good vision in the fellow eye have little difficulty with near and distance vision activities.



Source: Awdeh RM, Elsing SH, Deramo VA, et al. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Br J Ophthalmol 2010; 94: 319-323.

Reviewer's comments: The table 4 indicates that the NEI-VFQ near and distance vision scores are more correlated with visual acuity in the worse-seeing eye than in the better-seeing eye in patient with unilateral branch retinal vein occlusion (visual acuity was measured in logMAR units and therefore negative correlation implies positive relationship with the subscale). The lack of correlation with visual acuity in the better-seeing eye is curious, but could be due to the fact that 33/50 patients had excellent vision in the unaffected eye. Thus, any decrement in visual functioning was related to the vision in the worse-seeing eye. Awdeh et al (2010) concluded that "excellent visual acuity in the non-involved eye does not change the observation of BRVO associated with lower vision-related QOL scores shown in table 4". Although in Deramo et al (2003) study NEI-VFQ decrements were mostly correlated with vision in the better-seeing eye, these authors also concluded that decrements in the NEI-VFQ scores were observed in patients with unilateral central retinal vein occlusion even when visual acuity in the better-seeing eye is excellent. The findings from both studies support that the instrument is able to capture decrements in visual functioning in patients with unilateral disease.

Conclusions about psychometric validation:

Reviewer's comments:
Other measurement properties (construct validity, reliability, sensitivity to change) of the NEI-VFQ25 have been evaluated in patients with several ophthalmological conditions; however, limited evidence is available in the retinal vein occlusion population, but this limited information in general supports usefulness of the NEI-VFQ in the target population. The evidence by Deramo et al (2003), Awdeh et al (2010), and the sponsor's research suggest that cross-sectionally patients with retinal vein occlusion have little difficulty with near and distance vision activities. The studies by Deramo et al (2003) and Awdeh et al (2010) both demonstrated that the NEI-VFQ is able to capture decrements in vision-related quality of life due to RVO even

when visual acuity in the unaffected eye was excellent. See the next section regarding instrument sensitivity to change and evaluation of a responder definition.

7 INTERPRETATION OF SCORES

Sponsor states the following in their submission:

> "The data defining clinically important changes in NEI VFQ-25 scores in the literature are based largely on changes in VA in the better eye. Data show that VA changes in the worse eye are associated with smaller changes in NEI VFQ-25 scores compared with VA changes in the better eye. In the AREDS study, among patients with a loss of ≥ 15 letters in VA in their worse-seeing eye, there was a 4.9-point change in the VFQ-25 overall composite score, a 4.9-point change in the near activities score, and a 5.5-point change in the distance activities.(9) Data from a study by Cahill and colleagues showed that in patients with bilateral severe AMD undergoing macular translocation with 360-degree peripheral retinectomy, a 3-line change in distance VA in the operative eye corresponded to approximately 4.7 points on the VFQ-25 general vision, near vision activities, and distance vision activities subscale.(43) It is important to note that in the BRAVO and CRUISE trials, the vast majority of patients (over 90%) were treated in their worse-seeing eye. It is possible that a VA change of less than three lines may be important to both patients and clinicians and that the corresponding clinically important difference in the NEI VFQ-25 could be (b) (4)."

(b) (4)

Reviewer's comments:
The evidence submitted by the sponsor above suggest that 3-line changes in the worse-seeing eyes result in a smaller impact on patients' visual functioning than a similar change in the better-seeing eye. It is unknown, however, whether this smaller impact is clinically meaningful to the patients or not. Or is this simply a reflection that vision loss in the worse-seeing eye does not result in significant impact to the patient, hence the modest (b) (4) *Furthermore, none of this evidence comes from patients with retinal vein occlusion. The submission lacks empiric evidence using a patient-reported global anchor to determine what constitutes a clinically relevant change in the NEI-VFQ as it relates to changes in the worse-seeing eyes.*

The sponsor submitted the following table to describe the NEI-VFQ outcomes from their trials:

Table 6: Near and Distance Vision Activities Subscale Changes from Baseline to 6 Months: Randomized Subjects

			Ranibizumab	
Endpoint/Study		**Sham**	**0.3 mg**	**0.5 mg**
Improve ≥5 points for NEI VFQ-25 near - vision activities subscale				
BRAVO (FVF4165g)	N	129	133	130
	n (%)	67 (51.9%)	77 (57.9%)	88 (67.7%)
	95% CI of the % [a]	(43.3%, 60.6%)	(49.5%, 66.3%)	(59.7%, 75.7%)
	Difference in % (vs. sham) [b]		5.8%	16.3%
	95% CI of the difference [b]		(-6.1%, 17.7%)	(4.6%, 28.0%)
CRUISE (FVF4166g)	N	127	130	128
	n (%)	52 (40.9%)	70 (53.8%)	68 (53.1%)
	95% CI of the %	(32.4%, 49.5%)	(45.3%, 62.4%)	(44.5%, 61.8%)
	Difference in % (vs. sham) [b]		14.1%	13.3%
	95% CI of the difference [b]		(2.3%, 25.8%)	(1.4%, 25.3%)
Improve ≥5 points for NEI VFQ-25 distance-vision activities subscale				
BRAVO (FVF4165g)	N	129	133	130
	n (%)	57 (44.2%)	75 (56.4%)	80 (61.5%)
	95% CI of the %	(35.6%, 52.8%)	(48.0%,64.8%)	(53.2%, 69.9%)
	Difference in % (vs. sham) [b]		12.3%	17.3%
	95% CI of the difference [b]		(0.4%, 24.2%)	(5.4%, 29.2%)
CRUISE (FVF4166g)	N	127	130	128
	n (%)	44 (34.6%)	70 (53.8%)	55 (43.0%)
	95% CI of the %	(26.4%, 42.9%)	(45.3%, 62.4%)	(34.4%, 51.5%)
	Difference in % (vs. sham) [b]		19.2%	8.9%
	95% CI of the difference [b]		(7.4%, 31.1%)	(-2.9%, 20.7%)

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

[a] By normal approximation.

[b] Weighted estimates adjusting for the strata by using the Cochran-Mantel-Haenszel weights. Strata were defined using baseline VA score (≤34, 35 - 54, ≥55 letters).

Genentech, Inc.
Ranibizumab

Phase III Study: FVF4165g
Ranibizumab in BRVO

Table 14.2/8
Visual Function Scores (NEI VFQ-25): Mean and Mean Change from Baseline by Visit during the 6-Month Treatment Period (LOCF Method)
Randomized Subjects

Subscale or Composite / Visit / Treatment Group	N	Baseline Mean	Baseline (SD)	Baseline Median	Baseline Min	Baseline Max	Value at Visit Mean	Value at Visit (SD)	Value at Visit Median	Value at Visit Min	Value at Visit Max	Change from Baseline at Visit Mean	Change from Baseline at Visit (SD)	Change from Baseline at Visit (SE)	Change from Baseline at Visit Median	Change from Baseline at Visit Min	Change from Baseline at Visit Max
Near Activities																	
Day 0																	
Sham	129	69.6	(20.2)	70.8	8.3	100.0	69.6	(20.2)	70.8	8.3	100.0						
Ranibizumab 0.3 mg	133	67.9	(22.1)	70.8	0.0	100.0	67.9	(22.1)	70.8	0.0	100.0						
Ranibizumab 0.5 mg	130	69.4	(20.5)	75.0	8.3	100.0	69.4	(20.5)	75.0	8.3	100.0						
Month 1																	
Sham	129	69.6	(20.2)	70.8	8.3	100.0	74.1	(19.0)	75.0	12.5	100.0	4.5	(13.1)	(1.2)	4.2	-50.0	37.5
Ranibizumab 0.3 mg	133	67.9	(22.1)	70.8	0.0	100.0	75.6	(18.5)	79.2	25.0	100.0	7.6	(16.1)	(1.4)	4.2	-33.3	58.3
Ranibizumab 0.5 mg	130	69.4	(20.5)	75.0	8.3	100.0	76.9	(16.2)	79.2	29.2	100.0	7.5	(14.8)	(1.3)	4.2	-21.7	53.3
Month 3																	
Sham	129	69.6	(20.2)	70.8	8.3	100.0	75.8	(17.8)	75.0	12.5	100.0	6.2	(14.1)	(1.2)	7.5	-37.5	50.0
Ranibizumab 0.3 mg	133	67.9	(22.1)	70.8	0.0	100.0	76.9	(18.5)	79.2	16.7	100.0	8.9	(15.7)	(1.4)	8.3	-33.3	50.0
Ranibizumab 0.5 mg	130	69.4	(20.5)	75.0	8.3	100.0	79.3	(16.1)	83.3	33.3	100.0	10.0	(16.8)	(1.5)	8.3	-33.3	65.0
Month 6																	
Sham	129	69.6	(20.2)	70.8	8.3	100.0	76.9	(19.2)	83.3	25.0	100.0	7.3	(15.3)	(1.3)	8.3	-45.0	45.8
Ranibizumab 0.3 mg	133	67.9	(22.1)	70.8	0.0	100.0	80.0	(20.2)	87.5	4.2	100.0	12.1	(17.3)	(1.5)	8.3	-50.0	58.3
Ranibizumab 0.5 mg	130	69.4	(20.5)	75.0	8.3	100.0	83.1	(15.4)	87.5	33.3	100.0	13.7	(18.0)	(1.6)	11.3	-33.3	66.7

LOCF = Last observation carried forward. Baseline = Day 0. Scores range from 0 to 100; a higher score represents better functioning.

Source: Biostatistics(Walkyria) pgm(/ophth/fabv2/fvf4165g/current/programs/t_vfqmean_byvis)
Database (FINAL (29JUN2009). Program Verified.) Datasets (vfqlocf)
current : Generated 09NOV09 19:27 Page 1 of 13

Genentech, Inc.
Ranibizumab

Phase III Study: FVF4165g
Ranibizumab in BRVO

Table 14.2/8
Visual Function Scores (NEI VFQ-25): Mean and Mean Change from Baseline by Visit during the 6-Month Treatment Period (LOCF Method)
Randomized Subjects

Subscale or Composite / Visit / Treatment Group	N	Baseline Mean	Baseline (SD)	Baseline Median	Baseline Min	Baseline Max	Value at Visit Mean	Value at Visit (SD)	Value at Visit Median	Value at Visit Min	Value at Visit Max	Change from Baseline at Visit Mean	Change from Baseline at Visit (SD)	Change from Baseline at Visit (SE)	Change from Baseline at Visit Median	Change from Baseline at Visit Min	Change from Baseline at Visit Max
Distance Activities																	
Day 0																	
Sham	129	76.4	(20.6)	81.3	16.7	100.0	76.4	(20.6)	81.3	16.7	100.0						
Ranibizumab 0.3 mg	133	76.0	(20.5)	80.0	20.8	100.0	76.0	(20.5)	80.0	20.8	100.0						
Ranibizumab 0.5 mg	130	76.7	(18.1)	79.2	16.7	100.0	76.7	(18.1)	79.2	16.7	100.0						
Month 1																	
Sham	129	76.4	(20.6)	81.3	16.7	100.0	79.0	(20.1)	85.0	20.8	100.0	2.6	(13.9)	(1.2)	0.0	-45.8	65.8
Ranibizumab 0.3 mg	133	76.0	(20.5)	80.0	20.8	100.0	81.9	(17.8)	90.0	16.7	100.0	5.9	(13.1)	(1.1)	4.2	-25.0	62.5
Ranibizumab 0.5 mg	130	76.7	(18.1)	79.2	16.7	100.0	82.3	(15.8)	87.5	25.0	100.0	5.6	(14.2)	(1.2)	2.5	-25.0	45.8
Month 3																	
Sham	129	76.4	(20.6)	81.3	16.7	100.0	81.0	(18.4)	83.3	25.0	100.0	4.6	(14.4)	(1.3)	0.0	-25.0	70.0
Ranibizumab 0.3 mg	133	76.0	(20.5)	80.0	20.8	100.0	84.7	(16.7)	91.7	25.0	100.0	8.7	(16.0)	(1.4)	5.0	-40.0	70.8
Ranibizumab 0.5 mg	130	76.7	(18.1)	79.2	16.7	100.0	84.6	(16.4)	90.0	25.0	100.0	7.9	(16.0)	(1.4)	5.0	-30.0	58.3
Month 6																	
Sham	129	76.4	(20.6)	81.3	16.7	100.0	82.7	(18.2)	90.0	25.0	100.0	6.3	(15.0)	(1.3)	4.2	-26.7	65.8
Ranibizumab 0.3 mg	133	76.0	(20.5)	80.0	20.8	100.0	86.3	(17.2)	91.7	20.8	100.0	10.3	(17.2)	(1.5)	8.3	-29.2	79.2
Ranibizumab 0.5 mg	130	76.7	(18.1)	79.2	16.7	100.0	88.0	(14.0)	91.7	33.3	100.0	11.3	(16.6)	(1.5)	9.2	-33.3	58.3

LOCF = Last observation carried forward. Baseline = Day 0. Scores range from 0 to 100; a higher score represents better functioning.

Source: Biostatistics(Walkyria) pgm(/ophth/fabv2/fvf4165g/current/programs/t_vfqmean_byvis)
Database (FINAL (29JUN2009). Program Verified.) Datasets (vfqlocf)
current : Generated 09NOV09 19:27 Page 2 of 13

Genentech, Inc.
Ranibizumab

Phase III Study: FVF4166g
Ranibizumab in CRVO

Table 14.2/8
Visual Function Scores (NEI VFQ-25): Mean and Mean Change from Baseline by Visit during the 6-Month Treatment Period (LOCF Method)
Randomized Subjects

Subscale or Composite / Visit / Treatment Group	N	Baseline Mean	(SD)	Median	Min	Max	Value at Visit Mean	(SD)	Median	Min	Max	Change from Baseline at Visit Mean	(SD)	(SE)	Median	Min	Max
Near Activities																	
Day 0																	
Sham	127	69.9	(22.6)	75.0	0.0	100.0	69.9	(22.6)	75.0	0.0	100.0						
Ranibizumab 0.3 mg	130	71.2	(22.2)	75.0	0.0	100.0	71.2	(22.2)	75.0	0.0	100.0						
Ranibizumab 0.5 mg	128	70.7	(20.3)	75.0	5.0	100.0	70.7	(20.3)	75.0	5.0	100.0						
Month 1																	
Sham	127	69.9	(22.6)	75.0	0.0	100.0	70.6	(23.2)	75.0	0.0	100.0	0.7	(13.4)	(1.2)	0.0	-70.0	33.3
Ranibizumab 0.3 mg	130	71.2	(22.2)	75.0	0.0	100.0	77.5	(19.2)	81.3	16.7	100.0	6.3	(16.8)	(1.5)	4.2	-41.7	58.3
Ranibizumab 0.5 mg	128	70.7	(20.3)	75.0	5.0	100.0	75.2	(19.0)	79.2	16.7	100.0	4.4	(16.2)	(1.4)	4.2	-50.0	69.2
Month 3																	
Sham	127	69.9	(22.6)	75.0	0.0	100.0	74.7	(19.3)	79.2	16.7	100.0	4.8	(16.0)	(1.4)	4.2	-35.8	75.0
Ranibizumab 0.3 mg	130	71.2	(22.2)	75.0	0.0	100.0	78.6	(19.9)	83.3	8.3	100.0	7.5	(17.2)	(1.5)	4.2	-41.7	50.0
Ranibizumab 0.5 mg	128	70.7	(20.3)	75.0	5.0	100.0	78.3	(19.9)	87.5	12.5	100.0	7.5	(15.8)	(1.4)	4.2	-29.2	50.0
Month 6																	
Sham	127	69.9	(22.6)	75.0	0.0	100.0	75.0	(20.8)	79.2	16.7	100.0	5.1	(17.1)	(1.5)	4.2	-35.8	72.5
Ranibizumab 0.3 mg	130	71.2	(22.2)	75.0	0.0	100.0	81.4	(18.6)	87.5	4.2	100.0	10.2	(17.4)	(1.5)	8.3	-37.5	62.5
Ranibizumab 0.5 mg	128	70.7	(20.3)	75.0	5.0	100.0	80.0	(18.7)	83.3	20.8	100.0	9.3	(18.1)	(1.6)	8.3	-50.0	55.0

LOCF = Last observation carried forward. Baseline = Day 0. Scores range from 0 to 100; a higher score represents better functioning.

Source: Biostatistics(walkyria) pgm(/ophth/fabv2/fvf4166g/current/programs/t_vfsmean_byvis)
Database (FINAL (27JUL2009). Program Verified.) Datasets (vfqlocf)
current : Generated 11NOV09 17:12 Page 1 of 13

Genentech, Inc.
Ranibizumab

Phase III Study: FVF4166g
Ranibizumab in CRVO

Table 14.2/8
Visual Function Scores (NEI VFQ-25): Mean and Mean Change from Baseline by Visit during the 6-Month Treatment Period (LOCF Method)
Randomized Subjects

Subscale or Composite / Visit / Treatment Group	N	Baseline Mean	(SD)	Median	Min	Max	Value at Visit Mean	(SD)	Median	Min	Max	Change from Baseline at Visit Mean	(SD)	(SE)	Median	Min	Max
Distance Activities																	
Day 0																	
Sham	127	77.0	(22.5)	83.3	0.0	100.0	77.0	(22.5)	83.3	0.0	100.0						
Ranibizumab 0.3 mg	130	77.3	(19.8)	83.3	20.8	100.0	77.3	(19.8)	83.3	20.8	100.0						
Ranibizumab 0.5 mg	128	77.0	(19.7)	83.3	20.8	100.0	77.0	(19.7)	83.3	20.8	100.0						
Month 1																	
Sham	127	77.0	(22.5)	83.3	0.0	100.0	76.9	(22.7)	83.3	12.5	100.0	-0.1	(14.5)	(1.3)	0.0	-66.7	41.7
Ranibizumab 0.3 mg	130	77.3	(19.8)	83.3	20.8	100.0	81.1	(19.1)	87.5	20.8	100.0	3.8	(12.6)	(1.1)	2.5	-28.3	45.8
Ranibizumab 0.5 mg	128	77.0	(19.7)	83.3	20.8	100.0	80.6	(17.8)	83.3	25.0	100.0	3.5	(14.4)	(1.3)	0.0	-37.5	54.2
Month 3																	
Sham	127	77.0	(22.5)	83.3	0.0	100.0	79.5	(19.7)	83.3	16.7	100.0	2.5	(15.5)	(1.4)	0.0	-40.8	75.0
Ranibizumab 0.3 mg	130	77.3	(19.8)	83.3	20.8	100.0	83.6	(19.6)	91.7	8.3	100.0	6.3	(12.6)	(1.1)	4.2	-20.8	58.3
Ranibizumab 0.5 mg	128	77.0	(19.7)	83.3	20.8	100.0	83.3	(17.4)	87.5	29.2	100.0	6.2	(14.7)	(1.3)	4.2	-25.0	54.2
Month 6																	
Sham	127	77.0	(22.5)	83.3	0.0	100.0	79.8	(21.1)	87.5	16.7	100.0	2.8	(15.6)	(1.4)	0.0	-40.8	50.0
Ranibizumab 0.3 mg	130	77.3	(19.8)	83.3	20.8	100.0	86.2	(17.5)	91.7	8.3	100.0	8.9	(13.7)	(1.2)	8.3	-24.2	58.3
Ranibizumab 0.5 mg	128	77.0	(19.7)	83.3	20.8	100.0	83.7	(17.8)	90.0	20.8	100.0	6.7	(16.3)	(1.4)	4.2	-36.7	66.7

LOCF = Last observation carried forward. Baseline = Day 0. Scores range from 0 to 100; a higher score represents better functioning.

Source: Biostatistics(walkyria) pgm(/ophth/fabv2/fvf4166g/current/programs/t_vfsmean_byvis)
Database (FINAL (27JUL2009). Program Verified.) Datasets (vfqlocf)
current : Generated 11NOV09 17:12 Page 2 of 13

Reviewer's comments:

Up to a mean of 7.3-point (median of 8.3-point) improvement in near activities and up to a mean of 6.3-point (median of 4.2-point) improvement in distance activities were observed in the sham comparison group at 6 months one of the sponsor's (f4165g). A more conservative responder

definition should be chosen to have assurance that the effect observed is beyond an effect that could be a result of potential bias of subjects knowing the treatment assignment and beyond an improvement that might occur in the absence of treatment. It is also possible that patients are adjusting to their condition and that is why improvement is observed in the sham treatment arm. However, due to changes observed in the sham treatment arm, it is unlikely that a 4 to 5-point changes would constitute a clinically meaningful treatment benefit when that amount of change is observed without treatment.

The instrument itself is not without limitations and a small responder definition places much emphasis on instrument performance.

The mean and median change scores appear to be different in the tables above, the FDA statisticians should consider whether it is appropriate to use parametric methods to evaluate treatment efficacy. Should non-parametric methods be used? It is also noted herein that the NEI-VFQ scores are influenced by general health status of the patients and adjustment for general health should be considered when evaluating and interpreting NEI-VFQ scores.

So, what would be an appropriate responder definition for patients with RVO? This reviewer has explored various approaches to come up with a reasonable suggestion for a responder definition.

a) INSTRUMENT FACE VALUE

The response options and scoring of the NEI-VFQ:
No difficulty at all 100
A little difficulty 75
Moderate difficulty 50
Extreme difficulty 25
Stopped doing this because of your eyesight 0
Stopped doing this for other reasons or not interested in doing this scored as missing

At baseline, the patients in the sponsor's trials had near activities vision scores somewhere between 68 and 71; distance activities scores were between 76 and 77. These scores suggest that these patients have a little difficulty with their near and distance vision activities; a little more difficulty with near than distance vision. To show an improvement on one item, one would need a 25-point improvement. However, both near and distance vision subscales are 6-item scales. It would perhaps be unreasonable to expect 25-point improvement on every item on the scale. If half the items on the scale improve by 25-points then that would result in a 12.5-point improvement in the near and distance vision scale scores; if 2 of 6 items improve by 1-category then a 8.3-point improvement would be observed.

b) EMPIRIC EVIDENCE

- *Distribution-based methods*

In the sponsor's trials, the SD for baseline near activities scores ranged from 20 to 23 and for distance activities scores ranged from 18 to 22.

Similarly, in the sponsor's trials, the SD for 6-month change in near activities ranged from 15 to 18 and for distance activities ranged from 14 to 17.

Using well-known Cohen's estimates as guidance, ½ SD would be considered a moderate change.

Near activities scale
½ SD of baseline: 10-12.5 points
½ SD of 6-month change: 7.5-9 points

Distance activities
½ SD of baseline: 9-11 points
½ SD of 6-month change: 7-8.5 points

These findings suggest that a change of 7 to 12.5 points in the near and distance activities subscales may be meaningful to the subjects.

- *Anchor-based methods*

This reviewer is unaware of any publications that have looked at changes in the NEI-VFQ as compared to changes in visual acuity or changes in a patient-reported global anchor in patients with retinal vein occlusion. However, this has been looked at in other populations.

A study by Submacular Surgery Trials Research group (2007) that included 828 patients with subfoveal choroidal neovascularization secondary to AMD, ocular histoplasmosis, or idiopathic showed that a 3-line change in visual acuity in the better-seeing eye was associated with 6.6-point change in both near and distance vision subscales and 3-line change in the worse-seeing eye was associated with less than 2-point change in those same subscales. So, it appeared that changes in the near and distance vision functioning were mostly driven by changes in the better-eye visual acuity.

Recommendation for a responder definition

The limited evidence suggests that a change in near vision activities and distance vision activities subscales of 7 to 12.5 points may be clinically relevant; however, it is difficult to pinpoint an exact number from this range that might be clinically relevant. A 12.5-point change would represent, for example, a 1-category (25-point) improvement in 3 of 6 scale items. A 8.3-point change would represent, for example, a 1-category improvement in 2 of 6 scale items. A 12-5

point improvement would represent a value beyond the maximum change observed (at 6 months of follow-up) in the sham treatment arm.

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Sponsor submitted the following description of the translation process:

The interviewer-administered NEI VFQ-25 was developed in U.S. English and is available in a number of different languages. Mapi Research Institute performed a full linguistic validation on selected versions of the NEI VFQ-25 using the processes outlined below (Mapi Research Institute has adapted more than 200 questionnaires into more than 100 languages and has developed a standardized, internationally recognized translation procedure):(57)

1. Forward translation process:
    - Two independent forward translations of the original instrument were produced by two professional translators, native speakers of the language in question and fluent in English.
    - A meeting was held with the two translators and the consultant to produce a reconciled translation on the basis of the two forward translations.
2. Backward translation step:
    - A backward translation of the reconciled language version was produced in English by one professional translator, a native speaker of English and fluent in the country's language.
    - A meeting was held with the backward translator, one of the forward translators, and a consultant from Mapi Research Institute.
    - The backward translation was compared with the original and the discrepancies analyzed, resulting, if necessary, in changes in the reconciled translation and the subsequent production of a second translated version.
3. Proofreading:
    - The version obtained after the backward translation step was proofread by the consultant and by one translator, a native speaker of the country's language.
    - The proofreading results were discussed with the consultant, resulting in the final translated version.

Specifically, Genentech utilized the U.S. Spanish version of the questionnaire in their clinical trials (BRAVO and CRUISE). This version of the questionnaire also underwent an international harmonization process coordinated by the Mapi Research Institute. Translations were compared with one another and with the original during a meeting with translators representing each target language in order to ensure conceptual equivalence in all versions. Suggestions made during the international harmonization were discussed with the consultant, resulting in the fourth language version.

The psychometric properties of the U.S. Spanish version of the NEI VFQ-25 and -39 were assessed and compared with the U.S. English versions in a study that included 400 patients (160 Latinos and 243 non-Latinos from general ophthalmology clinics).(58)

In Latino patients, the near vision and distance vision activities subscales demonstrated adequate internal consistency reliability (Cronbach's alpha, 0.73 and 0.86, respectively). Results were similar for the NEI VFQ-25, demonstrating adequate internal consistency in Latino patients for the near vision and distance vision activities subscales (Cronbach's alpha, 0.88 and 0.90, respectively).(58)

Reviewer's comment: Sponsor did not submit translation and cultural adaptation protocols or detailed results of those studies to the Agency for review. SEALD recommends an exploratory evaluation of efficacy findings by language (i.e., English, Spanish) to evaluate variability in the response.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

REVIEW SUMMARY:

1. (b) (4)

2. (b) (4) Sponsor's 2009 qualitative research shows that issues related to near and distance reading activities are the most frequently reported concerns that patients with unilateral vision loss due to RVO experience; the other items included in the NEI-VFQ near and distance vision activities subscales were reported by these patients, although less frequently, and 2 items were not spontaneously reported at all (going down steps, stairs, or curbs in dim light or at night, difficulty figuring out whether bills are accurate); however, subjects acknowledge difficulty in those items in the

cognitive interviews. Reading computer screen (e.g., emails) was mentioned by the subjects as relevant, but it is not included in the NEI-VFQ. However, the instrument includes other items related to reading and it is unclear whether computer-related reading is really measuring a concept different from reading other print (e.g., ordinary print in newspapers) or not. Thus, there is some empiric evidence to support that the NEI-VFQ near and distance vision subscales include relevant items to the patients in the target population. Cognitive debriefing interviews suggested some interpretation issues with some of the instrument items (e.g., item on difficulty watching and enjoying programs on tv) and some of the response options. The qualitative research was not presented for subjects with central RVO and branch RVO separately and therefore it cannot be evaluated whether these subjects experience same or different vision-related issues or not. The DAIOP should consider that from their clinical perspective. Furthermore, no patients with bilateral visual impairment were enrolled in the qualitative research, although this may not be a major limitation considering that a relatively small number of patients with bilateral vision loss were enrolled in sponsor's phase 3 trials.

(b) (4)

(b) (4)

3. Information on NEI-VFQ's other measurement properties (i.e., construct validity, reliability, sensitivity to change) are important to determine whether the instrument adequately performs as a measurement tool. Limited amount of information on other measurement properties of the NEI-VFQ are available in the RVO population; however, that limited information generally supports usefulness of the instrument in the target population and generally is consistent with more extensive evaluation of NEI-VFQ measurement properties done in other ophthalmological conditions.

4. (b) (4)

(b) (4)

Recommendation for a responder definition:
The limited evidence suggests that a change in near vision activities and distance vision activities subscales of 7 to 12.5 points may be clinically relevant; however, it is difficult to pinpoint an exact number from this range. Based on instrument scoring, a 8.3-point change would represent, for example, a 1-category improvement in 2 of 6 scale items. A 12.5-point change would represent, for example, a 1-category (25-point) improvement in 3 of 6 scale items and a12.5-point change would be beyond the maximum median change observed (at 6 months of follow-up) in the sham treatment arm.

NEI-VFQ scores can be affected by general health status and adjustment for general health or comorbidities should be considered when evaluating treatment efficacy. Appropriateness of using parametric methods to evaluate treatment efficacy should be assessed (mean and median NEI-VFQ change scores appear different and suggest that the distributions may be skewed).

5. (b) (4)
(b) (4)

6. (b) (4)

7. Sponsor did not submit detailed information on NEI-VFQ translation process to Spanish. SEALD recommends an exploratory evaluation of efficacy findings by language (i.e., English, Spanish) to look for variability in the response.

10 KEY REFERENCES FOR INSTRUMENT

http://www.nei.nih.gov/resources/visionfunction/vfq_ia.pdf

http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf

Awdeh RM, Elsing SH, Deramo VA, et al. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Br J Ophthalmol 2010; 94: 319-323.

Deramo VA, Cox TA, Syed AB, et al. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2003; 121: 1297-1302.

Mangione CM, Berry S, Spritzer K, et al. Identifying the content area for the 51-item National Eye Institute Visual Function Questionnaire. Results from focus groups with visually impaired persons. Arch Ophthalmol 1998; 116: 227-233.

Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001; 119: 1050-1058.

Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Arch Ophthalmol 1998; 116: 1496-1504.

Submacular Surgery Trials Research Group. Evaluation of minimum clinically meaningful changes in scores on the National Eye Institute Visual Function Questionnaire (NEI-VFQ). SST Report Number 19. Ophthalmic Epidemiology 2007; 14: 205-215.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY GRACE LUBAO
08/01/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156/S053

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125156 | Supplement Number: 053 | NDA Supplement Type (e.g. SE5): SE6

Division Name: Division of Anti-Infective and Ophthalmology Products | PDUFA Goal Date: June 22, 2010 | Stamp Date: December 18, 2010

Proprietary Name: Lucentis

Established/Generic Name: ranibizumab injection

Dosage Form: injection

Applicant/Sponsor: Genentech, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) neovascular (wet) AMD
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of macular edema following retinal vein occlusion

': Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

ction A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

☒ Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

x Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

ction B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed^Δ
☐	Neonate	__ wk. __mo.	__ wk. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

ditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	__ yr. __ mo.	__ yr. __ mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

ediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	__ yr. __ mo.	__ yr. __ mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as propriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

in Citrix copy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

Our STN: BL 125156/S-053

March 5, 2010

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, California 94080-4990

Dear Dr. Rohrer:

This letter is in regard to your supplement to your biologics license application (BLA) dated December 18, 2009, received December 22, 2009, submitted under section 351 of the Public Health Service Act, for Lucentis (ranibizumab injection).

We have completed an initial review of your supplement to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your supplement. The review classification for this supplement is **Priority**. Therefore, the user fee goal date is June 22, 2010. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients. Once we have reviewed your request and the application we will notify you of our decision.

If you have any questions, call Lori Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

MD

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Copy

in Citrix

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125156/S-053

February 3, 2010

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, California 94080-4990

Dear Dr. Rohrer:

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Lucentis (ranibizumab injection):

STN	125156/S-053
Reason for the submission:	Additional indication for the treatment of Macular Edema Following Retinal Vein Occlusion
Date **of Supplement**:	December 18, 2009
Date of Receipt:	December 22, 2009
Action Due Date:	June 22, 2010

We consider this to be a **Prior Approval Supplement** (21 CFR 601.12(f)(1)) that requires CDER approval prior to distribution of product made using the changes.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have requested a full waiver from this requirement. We will notify you when a determination on the waiver request has been made.

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
http://www.fda.gov/oc/datacouncil/spl.html

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, call Lori Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

DRAFT COMMENTS PRIOR TO MEETING
Division of Anti-Infective and Ophthalmology Products

Meeting Date: July 13, 2009

Application: BLA 125,156
Drug: Lucentis (ranibizumab injection)
Sponsor: Genentech

Meeting Type: Pre Supplement new indication treatment of patients with macular edema secondary to retinal vein occlusion (RVO)

These draft comments are being given to as a courtesy prior to our formal meeting on July 13, 2009. If you understand our responses and feel they warrant no further discussion, the meeting could be cancelled. If you do wish to still have the meeting, please remember we will not entertain any new questions or documentation for that meeting. If you wish to discuss any new information another meeting request should be submitted.

QUESTIONS

1. Does the Agency agree that the proposed contents of the ranibizumab supplemental biologics application (sBLA) are sufficient for filing and review? In particular:

   a. Is our proposed plan for submission of Clinical Study Reports and Subject Narratives acceptable to the Agency?

Division Response: *Yes.*

   b. Is our proposed plan for submission of Case Report Forms (including images), datasets, and SAS programs acceptable to the Agency?

Division Response: *Yes.*

   c. Is our proposed plan for the Non-Clinical and Clinical Pharmacology section of the sBLA acceptable to the Agency?

Division Response: *Yes.*

   d. Is our proposed testing strategy for Anti-Therapeutic Antibodies acceptable to the Agency?

Division Response: *Yes.*

   e. Does the Agency have any other comments on the content of the ranibizumab RVO application?

Division Response: *As noted in the January 29, 2007, meeting, the protocols have design issues which may impact on the analysis.*

2. Is the Statistical Analysis Plan (SAP) for the Integrated Summary of Efficacy acceptable to the Agency?

Division Response: *There are not sufficient details in the plan to comment.*

3. Is the SAP for the Integrated Summary of Safety acceptable to the Agency?

Division Response: *There are not sufficient details in the plan to comment.*

4. For both of the Phase III studies FVF4165g and FVF4166g, the primary endpoint is at 6 months, and the RVO sBLA submission will be based on data from the 6-month treatment period of these studies. What are the Agency's expectations regarding submission of 12 month data from Studies FVF4165g and FVF4166g?

Division Response: *The Division expects a proposed timetable for the completion of the studies. It is expected that the results of studies FVF4165g and FVF4166g will be submitted as soon as they are available and in accordance with an agreed upon timetable.*

5. Does the Agency agree that the design and analysis of Studies FVF4165g and FVF4166g are capable of supporting the following additions to the LUCENTIS® USPI for the RVO indication:

a. [redacted] (b) (4)

[redacted]

– [redacted]

– [redacted]

[redacted]

Division Response: *No.*

6. If the safety and overall risk/benefit profiles of Lucentis in the RVO population (based on Studies FVF4165g and FVF4166g) are found to be consistent with those in the age-related macular degeneration (AMD) population, then Genentech does not plan to make any changes to the current risk management and safety monitoring activities. Does the Agency consider this approach reasonable?

Division Response: *The Division cannot determine whether changes are needed in the current risk management and safety activities until the supplemental application is submitted.*

7. Does the Agency approve the request for a Pediatric Waiver as provided?

Division Response: *Yes.*

8. As part of this sBLA, (b) (4)

(b) (4)

Division Response: *There is not sufficient information in the briefing package to be able to determine whether additional information is needed. A determination is expected to be made at the time of potential filing of the supplemental BLA.*

b. (b) (4)

Division Response: *Yes.*

c. (b) (4)

Division Response: *The Division expects a complete response to the deficiencies noted in the prior BLA supplement related* (b) (4)

9. (b) (4)

a. (b) (4)

Division Response: *Yes.*

b. Is there any additional information the FDA would require for (b) (4) If so, what information would be required?

Division Response: *There is not sufficient information in the briefing package to be able to determine whether additional information is needed. A determination of the completeness is expected to be made at the time of potential filing of the supplemental BLA. The impact of any potential bias due to the use of a sham in this study will also need to be considered.*

10. (b) (4)

(b) (4)

Division Response: *There is not sufficient information in the briefing package to be able to determine whether additional information is needed. A determination of the completeness is expected to be made at the time of potential filing of the supplemental BLA. The impact of any potential bias due to the use of a sham in this study will also need to be considered.*

11. Would the Agency like Genentech to provide it with a face-to-face technical walkthrough of the sBLA following submission? Specifically, we would provide the Agency with:
    - A Table of Contents with document descriptions as needed
    - A walkthrough of the submission in Global Submit with particular attention to specific constructs in the filing that may be unique

Division Response: *No, thank you. A face-to-face technical walkthrough is not necessary.*