CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125156Orig1s106

Trade Name:	Lucentis
Generic or Proper Name:	ranibizumab injection
Sponsor:	Genentech, Inc.
Approval Date:	February 6, 2015
Indication:	A vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with: Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy in patients with DME.

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125156Orig1s106

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	**X**
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125156/106

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Clara Cambon, PharmD
Program Management-IVO
1 DNA Way, MS 241B
South San Francisco, CA 94080-4990

Dear Dr. Cambon:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received August 7, 2014, submitted under section 351(a) of the Public Health Service Act for Lucentis (ranibizumab injection). We acknowledge receipt of your amendments dated November 5 and December 9, 2014 and February 5, 2015.

This Prior Approval supplemental biologics application provides for a new indication: treatment of Diabetic Retinopathy (DR) in patients with Diabetic Macula Edema (DME).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the labeling text submitted on February 5, 2015.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] 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 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA

has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] 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
Office of Prescription Drug Promotion
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. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Christina Marshall, Regulatory Project Manager, at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling and Carton

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
02/06/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

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 –
Diabetic Retinopathy in patients with Diabetic Macular Edema (1.4) 2/2015
Dosage and Administration – Diabetic Retinopathy in patients with Diabetic Macular Edema (2.5) 2/2015
Warnings and Precautions (5.3) 2/2015
Warnings and Precautions (5.4) 2/2015

----------INDICATIONS AND USAGE----------
LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, 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)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy in patients with DME (1.4)

----------DOSAGE AND ADMINISTRATION----------
For Ophthalmic Intravitreal Injection Only (2.1)

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

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment.

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Patients should be assessed regularly.

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

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema (2.4, 2.5)
- LUCENTIS 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

----------DOSAGE FORMS AND STRENGTHS----------
Single-use glass vial designed to provide 0.05 mL for intravitreal injections:
- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
- 6 mg/mL solution (LUCENTIS 0.3 mg) (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 following the injection (5.1).
- Increases in intraocular pressure (IOP) have been noted both pre- and post-intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors (5.3).
- Fatal events occurred more frequently in patients with DME and DR at baseline, who were treated monthly with LUCENTIS compared with control (5.4).

----------ADVERSE REACTIONS----------
- The most common adverse reactions (reported more frequently in LUCENTIS-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters, and increased IOP (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: 02/2015

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)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (Non Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR)) in patients with Diabetic Macular Edema (DME)

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 of 10 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the nine months after 3 initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly [*see Clinical Studies (14.1)*].

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly [*see Clinical Studies (14.1)*].

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) 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 6 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 Diabetic Macular Edema (DME)

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.5 Diabetic Retinopathy in patients with Diabetic Macular Edema

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.6 Preparation for Administration

Using aseptic technique, all 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 x 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.

2.7 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.

Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion of the optic nerve head immediately after the injection [*see Warnings and Precautions (5.2)*]. Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection [*see Warnings and Precautions (5.1)*].

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 for intravitreal injection.

- 10 mg/mL solution (LUCENTIS 0.5 mg)
- 6 mg/mL solution (LUCENTIS 0.3 mg)

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 following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.6, 2.7) and Patient Counseling Information (17)*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately [*see Dosage and Administration (2.7)*].

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 (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 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 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

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 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 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 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) [*see Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

In a pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

A pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the label:

- Endophthalmitis and Retinal Detachments
- Increases in Intraocular Pressure
- Thromboembolic Events
- Fatal Events in patients with DME and DR at baseline

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 detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience

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.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3, and 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline [*see Clinical Studies (14)*].

Safety data observed in Study AMD-4 were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

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

Table 1
Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritis	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2
Non-Ocular Reactions in the DME and DR, AMD and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	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%-9% 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 patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LUCENTIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

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 (12) 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

There are no studies of LUCENTIS in pregnant women. An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

Animal reproduction studies are not always predictive of human response. It is also not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab [*see Clinical Pharmacology (12.1)*], treatment with LUCENTIS may pose a risk to embryo-fetal development (including teratogenicity) and reproductive 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 have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 79% (2387 of 3005) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 54% (1636 of 3005) were ≥ 75 years of age [*see Clinical Studies (14)*]. 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.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

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, which lacks an Fc region, 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 (0.5 mg dose vial) or 6 mg/mL LUCENTIS (0.3 mg dose vial) 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 pathophysiology of neovascular AMD, macular edema following RVO, DR and DME. 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 retinal thickness (i.e., center point thickness (CPT) or central foveal thickness (CFT)), as assessed by optical coherence tomography (OCT) is associated with neovascular AMD, macular edema

following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD. Microvascular retinal changes and neovascularization, as assessed by color fundus photography, are associated with diabetic retinopathy.

Neovascular (Wet) Age-Related Macular Degeneration
In Study AMD-3, CPT was assessed by time domain (TD)-OCT in 118 of 184 patients. TD-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 in the sham group from baseline through Month 12. CPT decreased by Month 1 and decreased further at Month 3, on average. In this study, CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.1)*].

In Study AMD-4, CFT was assessed by spectral domain (SD)-OCT in all patients; on average, CFT reductions were observed beginning at Day 7 following the first LUCENTIS injection through Month 24. CFT data did not provide information capable of predicting final visual acuity results [see *Clinical Studies (14.1)*].

In patients treated with LUCENTIS, the area of CNV leakage, on average, decreased by Month 3 as assessed by FA. The area of CNV 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)*].

Diabetic Macular Edema
On average, CPT reductions were observed in Studies D-1 and D-2 beginning at Day 7 following the first LUCENTIS injection through Month 36. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.3)*].

Diabetic Retinopathy in patients with Diabetic Macular Edema
Improvements from baseline in DR severity as assessed on fundus photography were observed in Studies D-1 and D-2 at Month 3 (first scheduled DR photographic assessment after randomization) through Month 36 [*see Clinical Studies (14.4)*].

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 was more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration of 0.5 mg LUCENTIS, mean (±SD) maximum ranibizumab serum concentrations were 1.7 (± 1.1) ng/mL. These concentrations were below the concentration range of ranibizumab (11 to 27 ng/mL) that was necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay (based on human umbilical vein endothelial cells (HUVEC)). No significant change from baseline was observed in

the mean plasma VEGF concentrations following three monthly 0.5 mg intravitreal injections. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 2 mg/eye. Serum ranibizumab concentrations in RVO and DME and DR patients were similar to those observed in neovascular AMD patients.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, maximum serum concentrations 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.

In pharmacokinetic covariate analyses, 48% (520/1091) of patients had renal impairment (35% mild, 11% moderate, and 2% severe). Because the increases in plasma ranibizumab exposures in these patients are not considered clinically significant, no dosage adjustment is needed based on renal impairment status.

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. Although systemic exposure following ocular administration is expected to be low, effects on female fertility are possible due to the anti-VEGF mechanism of action for ranibizumab [*see Clinical Pharmacology (12.1)*].

14 CLINICAL STUDIES

Unless otherwise noted, visual acuity was measured at a distance of 4 meters.

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. Among LUCENTIS-treated patients, 31% to 37% 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 Table 3, Table 4, and Figure 1 below.

Table 3
Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n=229	LUCENTIS 0.5 mg n=230	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)	12	60%	91%	30% (23%, 37%)
	24	56%	89%	33% (26%, 41%)
Gain of ≥15 letters in visual acuity (%)	12	6%	31%	25% (18%, 31%)
	24	4%	30%	25% (18%, 31%)
Mean change in visual acuity (letters) (SD)	12	−11.0 (17.9)	+6.3 (14.1)	17.1 (14.2, 20.0)
	24	−15.0 (19.7)	+5.5 (15.9)	20.1 (16.9, 23.4)

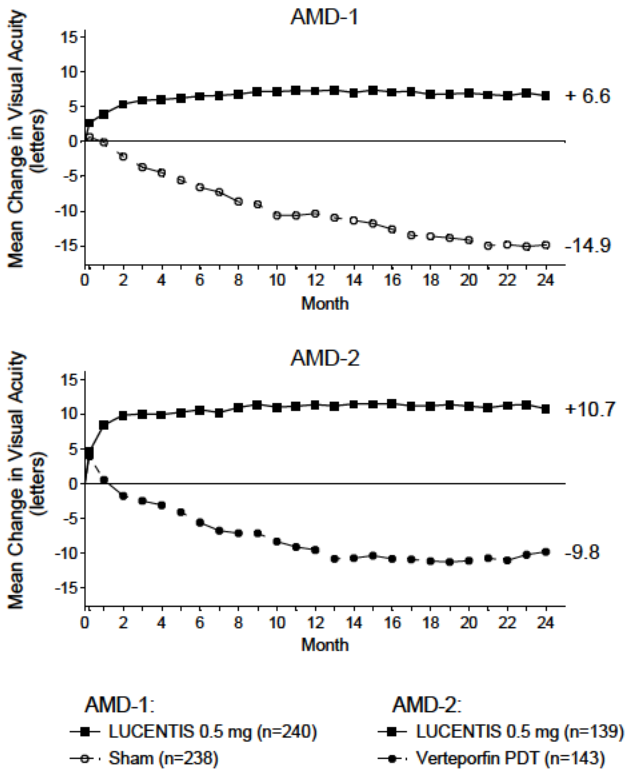
[a]Adjusted estimate based on the stratified model; $p < 0.01$

Table 4
Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfin PDT n=141	LUCENTIS 0.5 mg n=139	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)	12	66%	98%	32% (24%, 40%)
	24	65%	93%	28% (19%, 37%)
Gain of ≥15 letters in visual acuity (%)	12	11%	37%	26% (17%, 36%)
	24	9%	37%	29% (20%, 39%)
Mean change in visual acuity (letters) (SD)	12	–8.5 (17.8)	+11.0 (15.8)	19.8 (15.9, 23.7)
	24	–9.1 (18.7)	+10.9 (17.3)	20 (16.0, 24.4)

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

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



Visual acuity was measured at a distance of 2 meters

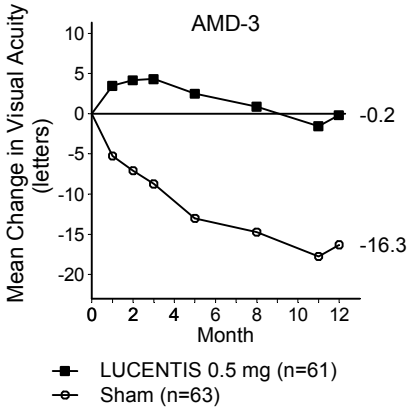
Patients in the group treated with LUCENTIS had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3 disc areas (DA) for LUCENTIS versus 2.3-2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV 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 3 months with LUCENTIS lost visual acuity, returning to

baseline at Month 12. In Study AMD-3, almost all LUCENTIS-treated patients (90%) lost fewer than 15 letters of visual acuity at Month 12.

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



Study AMD-4
Study AMD-4 was a randomized, double-masked, active treatment-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS 0.5 mg administered monthly or less frequently than monthly in patients with neovascular AMD. Patients randomized to the LUCENTIS 0.5 mg less frequent dosing arm received 3 monthly doses followed by monthly assessments where patients were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria. A total of 550 patients were enrolled in the two 0.5 mg treatment groups with 467 (85%) completing through Month 24. Data are available through Month 24.
Clinical results at Month 24 remain similar to that observed at Month 12.

From Month 3 through Month 24, visual acuity decreased by 0.3 letters in the 0.5 mg less frequent dosing arm and increased by 0.7 letters in the 0.5 mg monthly arm (see Figure 3). Over this 21 month period, patients in the 0.5 mg less frequent dosing and the 0.5 mg monthly arms averaged 10.3 and 18.5 injections, respectively. The distribution of injections received in the less frequent dosing arm is shown in Figure 4.

Figure 3

Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-4

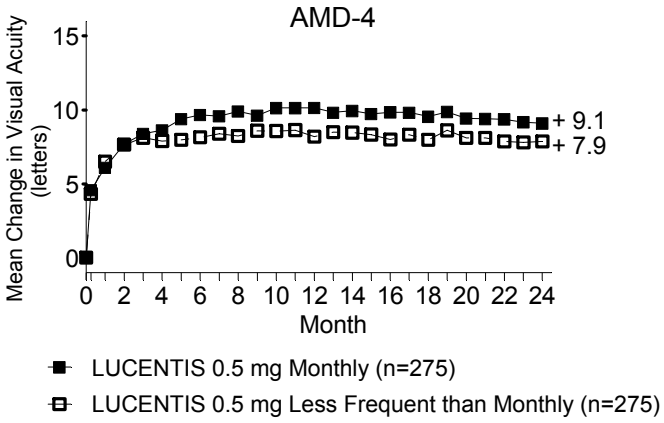
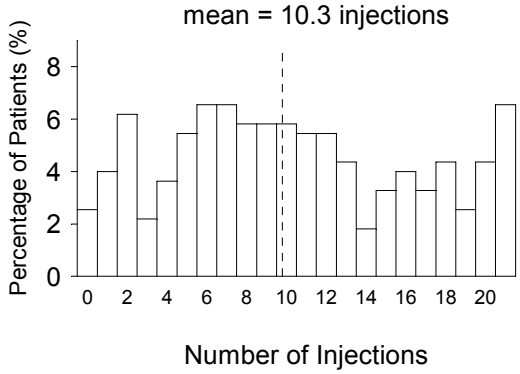


Figure 4

Distribution of Injections from Month 3 to Month 24 in the Less Frequent Dosing Arm in Study AMD-4



14.2 Macular Edema Following Retinal Vein Occlusion (RVO)

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 1-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 macular focal/grid laser treatment beginning at Month 3 of the 6-month treatment period. Macular focal/grid laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg LUCENTIS and 71 of 132 (54%) 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.

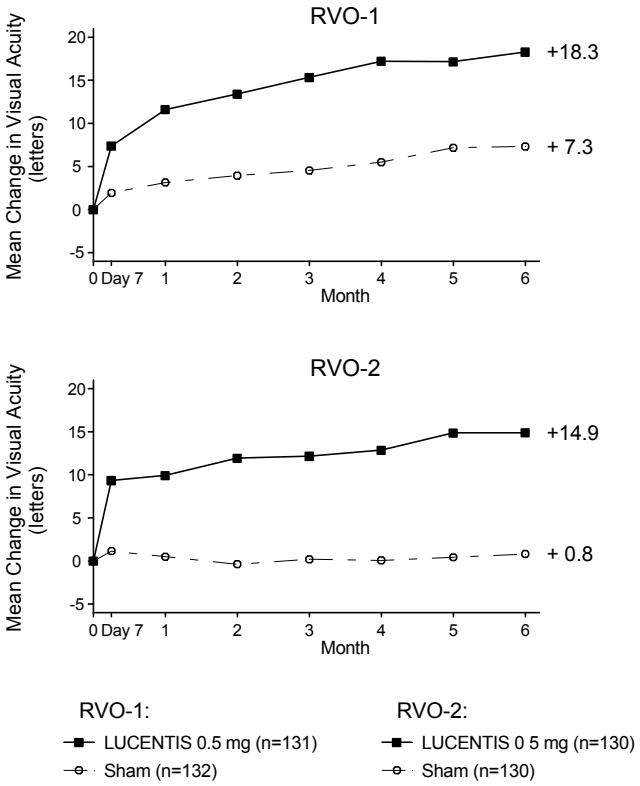
At Month 6, after monthly treatment with 0.5 mg LUCENTIS, the following clinical results were observed:

Table 5
Visual Acuity Outcomes at Month 6 in Study RVO-1 and Study RVO-2

Outcome Measure	Study [a]	Sham	LUCENTIS 0.5 mg	Estimated Difference (95% CI) [b]
Gain of ≥15 letters in visual acuity (%)	RVO-1	29%	61%	31% (20%, 43%)
Gain of ≥15 letters in visual acuity (%)	RVO-2	17%	48%	30% (20%, 41%)

[a] RVO-1: Sham, n=131; LUCENTIS 0.5 mg, n=132
RVO-2: Sham, n=130; LUCENTIS 0.5 mg, n=130
[b] Adjusted estimate based on stratified model; $p < 0.01$

Figure 5
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

14.3 Diabetic Macular Edema

Efficacy and safety data of LUCENTIS are derived from studies D-1 and D-2 (See Section 14.4 Diabetic Retinopathy below). All enrolled patients had DR and DME at baseline.

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 3-year studies. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (LUCENTIS 0.3 mg, 250 patients; LUCENTIS 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 582 (77%) completing through Month 36.

In Studies D-1 and D-2, patients received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly LUCENTIS 0.5 mg and patients originally randomized to monthly LUCENTIS 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with LUCENTIS 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with LUCENTIS 0.3 mg and 30 of 257 (12%) patients treated with sham.

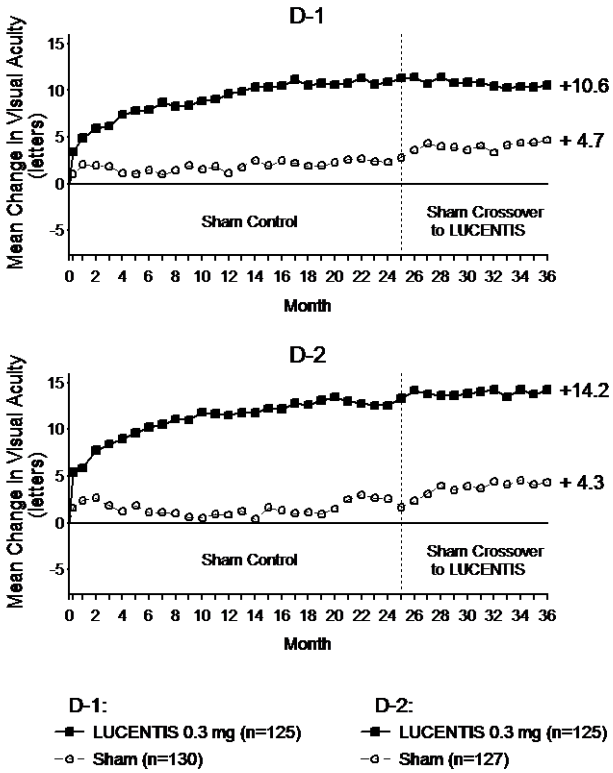
Compared to monthly LUCENTIS 0.3 mg, no additional benefit was observed with monthly treatment with LUCENTIS 0.5 mg. At Month 24, after monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed:

Table 6
Visual Acuity Outcomes at Month 24 in Study D-1 and D-2

Outcome Measure	Study[a]	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI)[b]
Gain of ≥15 letters in visual acuity (%)	D-1	12%	34%	21% (11%, 30%)
	D-2	18%	45%	24% (14%, 35%)
Loss of <15 letters in visual acuity (%)	D-1	92%	98%	7% (2%, 13%)
	D-2	90%	98%	8% (2%, 14%)
Mean change in visual acuity (letters)	D-1	2.3	10.9	8.5 (5.4, 11.5)
	D-2	2.6	12.5	9.6 (6.1, 13.0)

[a] D-1: Sham, n=130; LUCENTIS 0.3 mg, n=125
D-2: Sham, n=127; LUCENTIS 0.3 mg, n=125
[b] Adjusted estimate based on stratified model; $p \leq 0.01$

Figure 6
Mean Change in Visual Acuity from Baseline
to Month 36 in Study D-1 and Study D-2



p < 0.01 for all time points comparing LUCENTIS 0.3 mg to sham through Month 24

VA outcomes observed at Month 24 in patients treated with LUCENTIS 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the sham arms who received LUCENTIS 0.5 mg beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with LUCENTIS at the beginning of the studies.

In Studies D-1 and D-2, patients received monthly injections of LUCENTIS for 12 or 36 months, after which 500 patients opted to continue in the long-term follow-up study. Of 298 patients who had at least 12 months of follow-up from Month 36, 58 (19.5%) patients maintained vision with no further therapy. The remaining 202 patients were followed for less than 12 months.

14.4 Diabetic Retinopathy in patients with Diabetic Macular Edema (DME)
Efficacy and safety data of LUCENTIS are derived from studies D-1 and D-2 (See Section 14.3 Diabetic Macular Edema above). All enrolled patients had DR and DME at baseline.

Of the 759 patients enrolled, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study (ETDRS) Retinopathy Severity Scores (ETDRS-RSS) ranging from 10 to 75. At baseline, 62% of patients had NPDR (ETDRS-RSS less than 60) and 31% had PDR (ETDRS-RSS greater than or equal to 60).
The ETDRS-RSS could not be graded in 5% of patients at baseline, and 2% of patients had absent or questionable DR at baseline. Approximately 20% of the overall population had prior PRP.

After monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed (Table 7; Figure 7):

Table 7
≥3-step and ≥2-step improvement at Month 24 in
Study D-1 and Study D-2

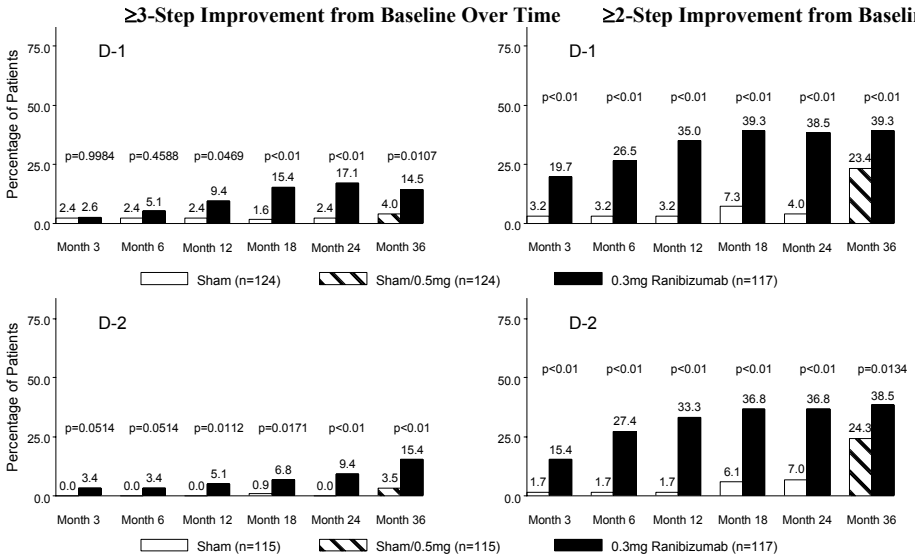
Outcome Measure	Study[a]	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI)[b]
≥3-step improvement from baseline in ETDRS-DRSS [c]	D-1	2%	17%	15% (7%, 22%)
	D-2	0%	9%	9% (4%, 14%)
≥2-step improvement from baseline in ETDRS-DRSS [d]	D-1	4%	39%	35% (26%, 44%)
	D-2	7%	37%	31% (21%, 40%)

[a] D-1: Sham, n=124; LUCENTIS 0.3 mg, n=117
D-2: Sham, n=115; LUCENTIS 0.3 mg, n=117
[b] Adjusted estimate based on stratified model
[c] $p < 0.05$ for all time points comparing LUCENTIS 0.3 mg to sham from Month 12 through Month 24
[d] $p < 0.05$ for all time points comparing LUCENTIS 0.3 mg to sham from Month 3 through Month 24

At Month 24, DR improvement by ≥3-steps in ETDRS-RSS from baseline in subgroups examined (e.g., age, gender, race, baseline visual acuity, baseline HbA1c, prior DME therapy at baseline, baseline DR severity (NPDR, PDR)) were generally consistent with the results in the overall population.

The difference in the proportion of patients treated with LUCENTIS 0.3 mg compared to sham who achieved DR improvement based on the ETDRS-RSS was observed as early as Month 3 for ≥2-step improvement or at Month 12 for ≥3-step improvement.

Figure 7
Proportion of Patients with ≥3-Step and ≥2-Step Improvement from Baseline in ETDRS Diabetic Retinopathy Severity Level over Time in Study D-1 and Study D-2



16 HOW SUPPLIED/STORAGE AND HANDLING

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-01) contains a single-use, 2-cc glass vial with a BLUE CAP designed to deliver 0.05 mL of 10 mg/mL ranibizumab.

- Each LUCENTIS 0.3 mg carton (NDC 50242-082-01) contains a single-use, 2-cc glass vial with a WHITE CAP designed to deliver 0.05 mL of 6 mg/mL ranibizumab.

In addition, each carton contains one 5-micron, 19-gauge x 1-1/2-inch filter needle for withdrawal of the vial contents; one 30-gauge x 1/2-inch injection needle for the intravitreal injection; and one package insert [*see Dosage and Administration (2.6)*]. 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

Advise patients that 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, advise the patient to 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	LUCENTIS® is a registered trademark of Genentech, Inc. ©2015 Genentech, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: sBLA 125156/S-106

The following officers/employees of participated in the decision to approve this application and consented to be identified.

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Philip Colangelo
William Boyd
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Christine Corser
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

OFFICE DIRECTOR MEMO

Deputy Division Director Review of BLA 125156/S-106

Date	February 6, 2015
From	Wiley A. Chambers, M.D.
BLA #	125156
Applicant	Genentech, Inc.
Date of Submission	August 7, 2014
Type of Application	Supplement 106
Name	Lucentis (ranibizumab injection)
Dosage forms / Strength	0.3% and 0.5% solution for intravitreal injection
Proposed New Indication(s)	For the treatment of diabetic retinopathy in patients with diabetic macular edema
Action:	Approval

1. Introduction

The applicant in this supplemental BLA initially requested the addition of an indication (b) (4) . The supplement did not include any new studies, but included a re-analysis of the two studies previously submitted to support the diabetic macular edema indication. During the review, the applicant revised the indication to the treatment of diabetic retinopathy in patients with diabetic macular edema. There are no drug products approved by the Food and Drug Administration for the (b) (4)

2. Background

BLA 125156 for Lucentis (ranibizumab injection) was approved on June 30, 2006, for the treatment of patients with neovascular (wet) age-related macular degeneration based primarily on the review of two Phase 3 studies (FVF2587g and FVF2598g). Supplemental BLA for Lucentis (ranibizumab injection) was approved on June 22, 2010, for the treatment of patients with macular edema following retinal vein occlusion. Supplemental BLA for Lucentis (ranibizumab injection), 0.3 mg approved on August 10, 2012, for the treatment of patients with diabetic macular edema.

Diabetic retinopathy (DR) may occur at any time during the course of diabetic mellitus as a complication of the diabetes. Early manifestations of the disease, sometimes referred to as non-proliferative diabetic retinopathy (NPDR), is characterized by microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts (called cotton wool spots), venous beading and intraretinal microvascular abnormalities. NPDR may progress to proliferative diabetic retinopathy (PDR) usually over a period of years and is characterized by growth of new, abnormal blood vessels (neovascularization) in the retina, optic disc, iris, and anterior chamber angle as a result of retinal ocular ischemia. PDR over the past 30+ years has been treated with laser intervention commonly referred to as panretinal photocoagulation (PRP) or surgical intervention with vitrectomy.

Studies FVF4168 g and FVF4170g enrolled patients with diabetic macular edema, a subset of patients with diabetic retinopathy (DR) patients. All enrolled patients had both diabetic retinopathy and diabetic macular edema. Because DME may occur in early or advanced DR, the patient populations enrolled in Studies FVF4168g and FVF4170g included a range of retinopathy severity levels.

3. CMC

There was no new chemistry/manufacturing/control data submitted in this supplement. Genentech requested a categorical exclusion from an Environmental Assessment in accordance with the criteria set forth in 21CFR §25.15 (d) and 25.31 (c). The applicant claimed that this supplement to a marketing approval of a biologic product meets the criteria for substances that occur naturally in the environment when the action does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment per 21 CFR §25.31(c). No additional environmental information is warranted and the request regarding the categorical exclusion from an Environmental Assessment is acceptable. The last facility compliance evaluation for (b) (4) (June 2014) was acceptable. Roche Singapore Technical Operations Pte. Ltd., 10 Tuas Bay Link, 637394 Singapore. FEI: 3007164129. The drug product release and stability testing facility was also found to be acceptable at it last inspection (December 2013). Novartis Pharma AG, Lichtstrasse 35 Switzerland. FEI: 3002807772.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted with this supplemental BLA. There are no revisions to the nonclinical sections of the previously approved labeling.

5. Clinical Pharmacology/Biopharmaceutics

No new serum pharmacokinetic data were submitted for review (apart for those already submitted and reviewed at the time of the NDA for the DME indication). The applicant proposed labeling changes (not specifically related to the new indication) under Section 12.3 Pharmacokinetics. These changes have been incorporated into the revised labeling.

6. Clinical/Statistical - Efficacy

Progression of DR on fundus photography is measured in discrete steps on the ETDRS DR Severity Scale. This scale is described in a publication of the Early Treatment in Diabetic Retinopathy Study Group in 1991. The DR anatomic worsening measured on the ETDRS scale has been shown to be associated with a clinically significant increase in the risk of visual loss.

Study	Design (Sites)	Population	Control	No. of Subjects Enrolled	Treatment Frequency and Duration	Dose(s)
FVF4168g (RIDE)	Multicenter, randomized, double-masked. Sham-controlled Months 1-24; Masked, Months 25-36; Open-label extension, up to Month 60. US and Latin America	Subjects with DR and DME	Sham injection for 24 months	382	Ranibizumab arms: intravitreal injections of 0.3 mg or 0.5 mg of ranibizumab q month during 36-month treatment period. Sham arm: sham injections q month for 25 months, after which subjects have the option to cross over to receive 0.5 mg ranibizumab at Month 25 (or earlier, if early treatment crossover criteria are met) for the remainder of the masked treatment period	0.3 mg (n=125) 0.5 mg (n=127) sham injection (n=130)
FVF4170g (RISE)				377		0.3 mg (n=125) 0.5 mg (n=125) sham injection (n=127)

DME = clinically significant macular edema with center involvement; DR = diabetic retinopathy

Main Efficacy Outcome Measure
For this re-analysis, the primary outcome measure was the proportion of subjects with a 3-step or greater improvement from baseline in the ETDRS diabetic retinopathy severity level at Month 24, as assessed by the central reading center using fundus photography (FP). The timepoint was chosen at Month 24 because it represented the end of sham-controlled study period. The Month 36 analysis served as supportive analysis because all sham subjects crossed over to receive 0.5-mg ranibizumab after Month 24.

As noted above, these studies were initially planned to support only a diabetic macular edema indication. Except for the proportion of subjects with a 3-step or greater worsening from baseline in the ETDRS diabetic retinopathy severity level as assessed by the central reading center using fundus photography, which was pre-specified as a secondary endpoint in the original study protocol, all analyses presented below were defined in the protocol as exploratory in nature. Family-wise type I error is not controlled among the DR-related analyses.

During the review of this supplemental application there was considerable debate over the potential strength and interpretation of data in which the type I error had not been controlled. At the time that the study had been planned, there was no expectation that diabetic retinopathy could be significantly reduced or improved. Prevention of progression was considered the best that could be accomplished.

Acceptance of the data in this case is based on the strength of the differences between groups in both two and three step changes, the biologic plausibility, and the data supporting the prior approval of related indications (Neovascular Age Related Macular Degeneration, Macular Edema secondary to Retinal Vein Occulsions and Diabetic Macular Edema). This case is not intended to serve as a precedent for other applications.

Study FVF4168g (RIDE)

Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
n (%)	3 (2.4%)	20 (17.1%)	21 (17.6%)
95% CI for percentage [a]	(0.0%, 5.1%)	(10.3%, 23.9%)	(10.8%, 24.5%)
Difference in % (vs. sham) [b]		14.5%	15.0%
95% CI of the difference [b]		(7.4%, 21.7%)	(7.8%, 22.2%)
p-value (vs. sham) [c]		0.0002	0.0001

Source: Module 5.3.5.3 ISE Table 12

Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).

a By normal approximation of the observed proportions;

b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Study FVF4170g (RISE)

Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24 (Subjects with a Valid Score at Baseline; LOCF)

	Sham n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=115
n (%)	0	11 (9.4%)	13 (11.3%)
95% CI for percentage [a]	(0.0%, 0.0%)	(4.1%, 14.7%)	(5.5%, 17.1%)
Difference in % (vs. sham) [b]		8.9%	11.7%
95% CI of the difference [b]		(4.0%, 13.7%)	(5.9%, 17.4%)
p-value (vs. sham) [c]		0.0014	0.0001

Source: Module 5.3.5.3 ISE Table 12

Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).

a By normal approximation of the observed proportions;

b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Randomized Subjects with a Valid Score at Baseline; LOCF) RIDE

	Sham n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
Month 24			
n (%)	5 (4.0%)	45 (38.5%)	43 (36.1%)
95% CI for percentage [a]	(0.6%, 7.5%)	(29.6%, 47.3%)	(27.5%, 44.8%)
Difference in % (vs. sham) [b]		34.8%	32.0%
95% CI of the difference [b]		(25.5%, 44.1%)	(22.8%, 41.2%)
p-value (vs. sham) [c]		<0.0001	<0.0001
	Sham/ 0.5 mg RBZ n=124	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=119**
Month 36			
n (%)	29 (23.4%)	46 (39.3%)	45 (37.8%)
95% CI for percentage [a]	(15.9%, 30.8%)	(30.5%, 48.2%)	(29.1%, 46.5%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		16.9%	14.3%
95% CI of the difference [b]		(5.5%, 28.3%)	(3.0%, 25.6%)
p-value (vs. sham) [c]		0.0058	0.0172

Source: Module 5.3.5.3 ISE Table 14

Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Subjects with a Valid Score at Baseline; LOCF) RISE

	Sham[a] / 0.5mg RBZ n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=115
Month 24			
n (%)	8 (7.0%)	43 (36.8%)	41 (35.7%)
95% CI for percentage [a]	(2.3%, 11.6%)	(28.0%, 45.5%)	(26.9%, 44.4%)
Difference in % (vs. sham) [b]		30.5%	28.3%
95% CI of the difference [b]		(20.9%, 40.2%)	(18.9%, 37.7%)
p-value (vs. sham) [c]		<0.0001	<0.0001
	Sham[a] / 0.5mg RBZ n=115	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=115**
Month 36			
n (%)	28 (24.3%)	45 (38.5%)	47 (40.9%)
95% CI for percentage [a]	(16.5%, 32.2%)	(29.6%, 47.3%)	(31.9%, 49.9%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		14.9%	17.6%
95% CI of the difference [b]		(3.6%, 26.2%)	(6.5%, 28.8%)
p-value (vs. sham) [c]		0.0134	0.0053

Source: Module 5.3.5.3 ISE Table 14

Efficacy Summary
Post hoc analyses of these studies demonstrate safety and efficacy of ranibizumab 0.3-mg injection in the treatment diabetic retinopathy in patients with diabetic macular edema.

7. Safety

No new safety data are presented in the original supplemental application. The 4 month Safety Update was submitted on November 5, 2014. This safety update contains no new data.

8. Advisory Committee Meeting/Regulatory Briefing

AC MEETING
No Advisory Committee Meeting was held for this supplemental application. The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration did meet on July 26, 2012, at the FDA White Oak Campus, Silver Spring, MD, for the diabetic macular edema indication. The committee unanimously agreed that substantial evidence of efficacy has been provided to demonstrate that Lucentis (ranibizumab injection) was effective for the treatment of diabetic macular edema. Please see the transcript for details of the Committee discussion.

REG BRIEFING
This supplemental application was presented at a CDER Regulatory Briefing on January 23, 2015.

9. Pediatrics

Diabetic retinopathy in patients with diabetic macular edema very rarely occurs in the pediatric age group. Therefore, a pediatric waiver was sought and granted for this indication. The supplemental application was presented at the PeRC PREA Subcommittee Meeting on November 5, 2014, where PeRC agreed with a full waiver because studies would be impossible or highly impracticable.

10. Other Relevant Regulatory Issues

OSI
An Office of Scientific Investigations (OSI) audit was requested and performed for the two Phase 3 studies (FVF2587g and FVF2598g for the diabetic macular edema indication. No new inspections were requested for this new supplemental application.

FINANCIAL DISCLOSURE
This submission contains post hoc analyses of data from Studies FVF4168g and FVF4170g originally submitted in S-076 which was approved August 10, 2012. Genentech provided adequate financial disclosure information for Studies FVF4168g and FVF4170g during the review of S-076 approved August 10, 2012.

11. Labeling

Revised labeling for BLA 125156 for Lucentis (ranibizumab injection), Supplement 106, was submitted by Genetech, Inc., on February 5, 2015.

12. Regulatory Action

BLA 125156 for Lucentis (ranibizumab injection), Supplement 106, will be approved for the treatment of diabetic retinopathy in patients with diabetic macular edema with the package insert labeling submitted by Genetech, Inc., on February 5, 2015.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
02/06/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 5, 2015
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	125156
Applicant	Genentech, Inc.
Date of Submission	August 7, 2014
PDUFA Goal Date	February 6, 2015
Type of Application	Supplement 106
Name	Lucentis (ranibizumab injection)
Dosage forms / Strength	0.3% and 0.5% solution for intravitreal injection
Proposed New Indication(s)	For the treatment of diabetic retinopathy in patients with diabetic macular edema
Recommended:	Recommended for Approval

1. Introduction

This supplemental BLA includes clinical information to support revision of the Lucentis U.S. Package Insert to include the new indication treatment of diabetic retinopathy in patients with diabetic macular edema. (b) (4)

The 24-Month Clinical Study Reports for Studies FVF4168g and FVF4170g, "A Phase 3, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus" and the "Month 36 Safety and Efficacy Data for Studies FVF4168g and FVF4170g," were resubmitted within this Supplemental BLA 125156.

There are no intravitreally administered drug products approved by the Food and Drug Administration for the treatment of treatment of diabetic retinopathy in patients with diabetic macular edema. There are no drug products approved for the (b) (4) .

2. Background

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.

Reference is also made to the Supplemental BLA for Lucentis (ranibizumab injection) approved on June 22, 2010, for the treatment of patients with macular edema following retinal vein occlusion. Reference is also made to the Supplemental BLA for Lucentis (ranibizumab injection), 0.3 mg approved on August 10, 2012, for the treatment of patients with diabetic macular edema.

In this supplemental BLA, Genentech seeks to update the Lucentis labeling with a new indication. (b) (4)

On May 20, 2014, a Type-B, pre- sBLA meeting was held to discuss the acceptability of the retinopathy data from Studies FVF4168g and FVF4170g (b) (4) . In preliminary responses, the Division agreed that the proposed efficacy and safety data from the studies appeared to be adequate (b) (4) The Division also agreed with the proposed Statistical Analysis Plan for the Integrated Summary of Efficacy. Genentech was satisfied with the responses and cancelled the meeting.

On July 17, 2014, Genentech submitted an initial Pediatric Study Plan (PSP) to IND 8633 within 60 days of the planned pre-sBLA meeting.

Diabetic retinopathy (DR) may occur at any time during the disease course as a complication of both Type 1 and Type 2 diabetes mellitus. The earliest manifestation of the disease, early non-proliferative diabetic retinopathy (NPDR), is characterized by microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts (called cotton wool spots), and, in more severe cases, venous beading and intraretinal microvascular abnormalities which are visualized on ophthalmoscopic examination or retinal photography. NPDR may progress to proliferative diabetic retinopathy (PDR) usually over a period of years and is characterized by growth of new, abnormal blood vessels (neovascularization) in the retina, optic disc, iris, and anterior chamber angle as a result of retinal ocular ischemia and the resultant increase in VEGF levels. The progression through NPDR and PDR is serious and represents clinically significant progression of the disease pathology to the advanced stages of the disease. PDR traditionally has been treated with laser intervention with panretinal photocoagulation (PRP) or surgical intervention with vitrectomy.

Studies FVF4168 g and FVF4170g enrolled patients with diabetic macular edema which is the leading cause of vision loss in diabetic retinopathy (DR) patients. All enrolled patients had both diabetic retinopathy and diabetic macular edema. Because DME may occur in early or advanced DR, the patient populations enrolled in Studies FVF4168g and FVF4170g included a range of retinopathy severity levels.

Progression of DR is measured in discrete steps as described by the ETDRS DR Severity Scale[1]. This scale is well established for objective quantification of retinopathy severity and a validated method for quantification of DR change. The DR anatomic worsening measured on the ETDRS scale has been shown to be associated with a clinically significant increase in the risk of visual loss.[2]

While Studies FVF4168g and FVF4170g were designed to evaluate the effects of ranibizumab on outcome measures associated with DME (e.g., changes over time in best corrected visual acuity [BCVA]), they also followed the improvement or worsening of the underlying DR symptoms on the ETDRS DR severity scale based on fundus photographs that were obtained at pre-specified time points and evaluated by an independent reading center. Evaluators of DR severity were masked to treatment assignment and all photographs were evaluated according to protocol specific criteria.

1 Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study Design and Baseline Patient Characteristics. ETDRS Study Report 7. Ophthamology 1991; 98:741-756.
2 The Diabetic Retinopathy Study Research Group. Four Risk Factors for Severe Visual Loss in Diabetic Retinopathy. The Third Report from the Diabetic Retinopathy Study. Arch Ophthalmol 1979; 97:654-655.

3. CMC

There is no new chemistry/manufacturing/control data submitted in this supplement. From the Office of Biotechnology, Division of Monoclonal Antibodies, Memorandum of Review dated October 29, 2014:

Genentech is requesting a categorical exclusion from an Environmental Assessment in accordance with the criteria set forth in 21CFR §25.15 (d) and 25.31 (c). The applicant claims that this supplement to a marketing approval of a biologic product meets the criteria for substances that occur naturally in the environment when the action does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment per 21 CFR §25.31(c).

There is no information in this supplement indicating that any additional environmental information is warranted. The applicant's request regarding the categorical exclusion from an Environmental Assessment is acceptable.

The facility compliance evaluation for (b) (4) is acceptable.

Manufacturing Location: Singapore
Firm Name: Roche Singapore Technical Operations Pte. Ltd.
Address: 10 Tuas Bay Link, 637394
FEI: 3007164129
Short summary of manufacturing activities performed: Drug Substance Manufacturing, Certificate of Analysis Release, and Stability Testing

This site was inspected by IOG from 6/16/2014 – 6/24/2014 and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance manufacturing operations. The TRP profile was updated and is acceptable.

Manufacturing Location: Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35
FEI: 3002807772
Short summary of manufacturing activities performed: Drug Product Release, and Stability Testing

This site was inspected by IOG from 12/2/2013 – 12/5/2013 and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The CTB profile was updated and is acceptable. There are no pending or ongoing compliance actions that prevent approval of this supplement.

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology review dated January 14, 2015: No new nonclinical studies were submitted with this supplemental BLA. There are no revisions to the nonclinical sections of the previously approved label. As such, there are no new concerns/recommendations from the nonclinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review dated October 16, 2014: No new serum pharmacokinetic data were submitted for review (apart for those already submitted and reviewed at the time of the NDA for the DME indication). In addition, the applicant has proposed labeling changes (not specifically related to the new indication) under Section 12.3 Pharmacokinetics.

The reviewer's recommended labeling edits are found below. The maximum serum ranibizumab concentration (0.3 ng/mL to 2.36 ng/mL) was updated to the mean value (b) (4) as reported by Avery and coworkers (2014). It is recommended that the current ranibizumab IC50 for VEGF inhibition (11 to 27 ng/mL) be retained until data based on a human retinal cell line become available for review.

Based on the serum ranibizumab concentration data from the HARBOR trial, it is recommended that the range for dose proportionality of serum ranibizumab concentrations be extended from 1 mg/eye to 2 mg/eye.

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 was more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration of 0.5 mg Lucentis, the mean (± SD) maximum serum ranibizumab concentration was 1.7 (± 1.1) ng/mL. These concentrations were below the concentration range of ranibizumab (11 to 27 ng/mL) that was necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an *in vitro* cellular proliferation assay (based on human umbilical vein endothelial cells (HUVEC)). No significant change from baseline was observed in the mean plasma VEGF concentrations following three monthly 0.5 mg intravitreal injections. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 2 mg/eye. Serum ranibizumab concentrations in RVO and DME and DR patients were similar to those observed in neovascular AMD patients.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, maximum serum concentrations 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.

In pharmacokinetic covariate analyses, 48% (520/1091) of patients had renal impairment (35% mild, 11% moderate, and 2% severe). Because the increases in plasma ranibizumab exposures in these patients are not considered clinically significant, no dosage adjustment is needed based on renal impairment status.

6. Sterility Assurance

There is no new chemistry/manufacturing/control data submitted in this supplement.

7. Clinical/Statistical - Efficacy

From the Medical Officer Review finalized January 29, 2015:
Studies FVF4168 g and FVF4170g, enrolled patients with diabetic macular edema, a retinal condition which is the leading cause of vision loss in patients with DR.[3] All of the patients enrolled in these studies had DR and DME. While the patients were followed for changes in diabetic macular edema, they were also evaluated for changes to their underlying DR.

Progression of DR on fundus photography is measured in discrete steps on the ETDRS DR Severity Scale. This scale is described in a publication of the Early Treatment in Diabetic Retinopathy Study Group in 1991. The DR anatomic worsening measured on the ETDRS scale has been shown to be associated with a clinically significant increase in the risk of visual loss.

Study	Design (Sites)	Population	Control	No. of Subjects Enrolled	Treatment Frequency and Duration	Dose(s)
FVF4168g (RIDE)	Multicenter, randomized, double-masked. Sham-controlled Months 1-24; Masked, Months 25-36; Open-label extension, up to Month 60. US and Latin America	Subjects with CSME-CI secondary to DM	Sham injection for 24 months	382	Ranibizumab arms: intravitreal injxns of 0.3 mg or 0.5 mg of ranibizumab q month during 36-month tx period Sham arm: sham injxns q month for 25 months, after which subjects have the option to cross over to receive 0.5 mg ranibizumab at Month 25 (or earlier, if early treatment crossover criteria are met) for the remainder of the masked treatment period	0.3 mg (n=125) 0.5 mg (n=127) sham injxn (n=130)
FVF4170g (RISE)				377		0.3 mg (n=125) 0.5 mg (n=125) sham injxn (n=127)

CSME-CI = clinically significant macular edema with center involvement; DM = diabetes mellitus

Statistical Analysis Plan (b) (4)

(b) (4) **Outcome Measures**

The main analysis was based on Month 24 data since this was the sham-controlled study period. The Month 36 analysis serves as supportive analysis because sham subjects crossed over to receive 0.5-mg ranibizumab after Month 24 and pure sham-controlled data was no longer available.

Main Efficacy Outcome Measure

3 Johnson, MW. Etiology and Treatment of Macular Edema. Am J Ophthalmol 2009; 147:11-21.

Proportion of subjects with a 3-step or greater improvement from baseline in the ETDRS diabetic retinopathy severity level at Month 24, as assessed by the central reading center using fundus photography (FP).

*****See the Medical Officer Review for the supplemental application finalized January 29, 2015, for extensive protocol descriptions, analysis plans, and secondary endpoints. *****

Except for the proportion of subjects with a 3-step or greater worsening from baseline in the ETDRS diabetic retinopathy severity level as assessed by the central reading center using fundus photography which was pre-specified in the original study protocol all analyses are exploratory in nature. Family-wise type I error is not strongly controlled among the DR-related analyses.

Study FVF4168g (RIDE)

Table 6.1.1.4-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
n (%)	3 (2.4%)	20 (17.1%)	21 (17.6%)
95% CI for percentage [a]	(0.0%, 5.1%)	(10.3%, 23.9%)	(10.8%, 24.5%)
Difference in % (vs. sham) [b]		14.5%	15.0%
95% CI of the difference [b]		(7.4%, 21.7%)	(7.8%, 22.2%)
p-value (vs. sham) [c]		0.0002	0.0001

Source: Module 5.3.5.3 ISE Table 12
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Study FVF4170g (RISE)

Table 6.1.2.4-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24 (Subjects with a Valid Score at Baseline; LOCF)

	Sham n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=115
n (%)	0	11 (9.4%)	13 (11.3%)
95% CI for percentage [a]	(0.0%, 0.0%)	(4.1%, 14.7%)	(5.5%, 17.1%)
Difference in % (vs. sham) [b]		8.9%	11.7%
95% CI of the difference [b]		(4.0%, 13.7%)	(5.9%, 17.4%)
p-value (vs. sham) [c]		0.0014	0.0001

Source: Module 5.3.5.3 ISE Table 12
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Efficacy Summary Statement

The 24-Month Clinical Study Reports for Studies FVF4168g and FVF4170g, "A Phase 3, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus" and the "Month 36 Safety and Efficacy Data for Studies FVF4168g and FVF4170g," were resubmitted within this Supplemental BLA 125156. Post hoc analyses of these studies demonstrate safety and efficacy of ranibizumab 0.3-mg injection in the treatment of patients with diabetic retinopathy. The two Phase 3 studies demonstrate replicative results in the ability of intravitreal ranibizumab when given every four weeks (approximately every 28 days) to improve diabetic retinopathy based on the ETDRS diabetic retinopathy severity scale (DRSS) compared to sham treatment. These trials included a sham treatment arm.

The submitted analyses demonstrate that patients who were treated with intravitreal ranibizumab 0.3-mg every four weeks (approximately 28 days) experienced a greater than or equal to 3-step improvement based on the ETDRS Diabetic Retinopathy Severity Scale when compared to sham treatment.

8. Safety

From the Medical Officer Review finalized January 29, 2015:

No new safety data are presented in the original supplemental application. The 4 month Safety Update was submitted on November 5, 2014. This safety update contains no new data.

Safety Summary Statement

The 24-Month Clinical Study Reports submitted within this Supplemental BLA 125156 for Studies FVF4168g and FVF4170g, "A Phase 3, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus" and the "Preliminary Report: Month 36 Safety and Efficacy Data for Studies FVF4168g and FVF4170g" together demonstrate the safety profile of both ranibizumab 0.3-mg and 0.5-mg injection in the treatment of diabetic retinopathy in patients with diabetic macular edema.

9. Advisory Committee Meeting/Regulatory Briefing

AC MEETING
No Advisory Committee Meeting was held for this supplemental application. The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration did meet on July 26, 2012, at the FDA White Oak Campus, Silver Spring, MD, for the diabetic macular edema indication. The committee unanimously agreed that substantial evidence of efficacy has been provided to demonstrate that Lucentis (ranibizumab injection) was effective for the treatment of diabetic macular edema. Please see the transcript for details of the Committee discussion.

REG BRIEFING
This supplemental application was presented at a CDER Regulatory Briefing on January 23, 2015.

The group was asked their opinion of the evidence of efficacy for the treatment of DR in patients with DME; they were specifically asked if they recommended including a new indication in the Indications and Usage section of the label, "treatment of DR in patients with DME" and describing the efficacy results in the Clinical Studies section of the labeling. There was a unanimous conclusion that the new indication be included. (b) (4)

10. Pediatrics

Diabetic retinopathy in patients with diabetic macular edema very rarely occurs in the pediatric age group. Therefore, a pediatric waiver was sought and granted for this indication. The supplemental application was presented at the PeRC PREA Subcommittee Meeting on November 5, 2014, where PeRC agreed with a full waiver because studies would be impossible or highly impracticable.

11. Other Relevant Regulatory Issues

OSI
An Office of Scientific Investigations (OSI) audit was requested and performed for the two Phase 3 studies (FVF2587g and FVF2598g for the diabetic macular edema indication. No new inspections were requested for this new supplemental application.

FINANCIAL DISCLOSURE
This submission contains post hoc analyses of data from Studies FVF4168g and FVF4170g originally submitted in S-076 which was approved August 10, 2012. Genentech provided adequate financial disclosure information for Studies FVF4168g and FVF4170g during the review of S-076 approved August 10, 2012.

BIOSTATISTICS
Per the Biostatistics review dated January 15, 2015:

According to the submission, the main analysis to support the [redacted] (b) (4) was the proportion of subjects who experienced a ≥ 3-step improvement from baseline in DR severity scale at Month 24 during the sham-controlled period of the study. Subjects treated with ranibizumab demonstrated improvements in DR severity scale in both studies. At Month 24, the proportion of subjects who experienced a ≥ 3-step improvement in DR severity scale in the 0.3 mg ranibizumab group was 17.1% and 9.4%, versus 2.4% and no subjects in the sham group, in Study FVF4168g and Study FVF4170g, respectively. The majority of the subjects who achieved a 3-step improvement in DR severity scale at Month 24 had moderately severe NPDR, severe NPDR, or mild PDR at baseline; a ≥ 3-step improvement translated into a transition from severe NPDR to less severe NPDR or a reversal from high-risk PDR to mild NPDR.

The protocols defined the proportion of subjects who achieved a ≥ 3-step progression from baseline in the DR severity level at 24 months as a secondary efficacy endpoint. Statistical significance was not demonstrated in the individual studies for the comparison of 0.3 mg ranibizumab group with the sham group with respect to this DR endpoint, likely due to the low incidence of a ≥ 3-step progression and inadequate number of subjects. However, a favorable trend was observed for ranibizumab treatment in slowing DR progression.

An improvement of ≥ 3-step in the DR severity scale was not a pre-specified endpoint in the study protocols. However, it was considered a valid measurement for the clinical benefit of DR therapy and a similarly defined endpoint (an improvement of ≥2 steps in the DR severity scale) had been used in the clinical studies of another anti-VEGF product. Therefore, the treatment effect observed in the endpoint of an improvement of ≥ 3-step in the DR severity scale was unlikely due to chance,

12. Labeling

BLA 125156 for Lucentis (ranibizumab injection), Supplement 106, is recommended for approval for the treatment of diabetic retinopathy in patients with diabetic macular edema with the package insert labeling submitted by Genetech, Inc., on 2/05/2015 and found in this CDTL review (see Appendix 1).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
BLA 125156 for Lucentis (ranibizumab injection), Supplement 106, is recommended for approval for the treatment of diabetic retinopathy in patients with diabetic macular edema with the package insert labeling submitted by Genetech, Inc., on 2/05/2015 and found in this CDTL review (see Appendix 1).

The 24-Month Clinical Study Reports for Studies FVF4168g and FVF4170g, "A Phase 3, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus" and the "Month 36 Safety and Efficacy Data for Studies FVF4168g and FVF4170g," were resubmitted within this Supplemental BLA 125156. Post hoc analyses of these studies demonstrate safety and efficacy of ranibizumab 0.3-mg injection in the treatment of patients with diabetic retinopathy. The two Phase 3 studies demonstrate replicative results in the ability of intravitreal ranibizumab when given every four weeks (approximately every 28 days) to improve diabetic retinopathy based on the ETDRS diabetic retinopathy severity scale (DRSS) compared to sham treatment. These trials included a sham treatment arm.

The approval of this supplemental application based on post hoc analyses should not be construed as precedent setting. This is an unusual circumstance [redacted] (b) (4). An improvement of ≥ 3-step in the DR severity scale was not a pre-specified endpoint in the study protocols, but it is considered a valid measurement for the clinical benefit of [redacted] (b) (4). Future controlled trials with a sham would now be considered unethical based on the results of Studies FVF4168g and FVF4170g in the treatment of diabetic retinopathy in patients with diabetic macular edema.

RISK BENEFIT ASSESSMENT:
The benefits of Lucentis (ranibizumab injection) 0.3 mg for the recommended indication outweigh the associated risks.

The 24-Month Clinical Study Reports submitted within this Supplemental BLA 125156 for Studies FVF4168g and FVF4170g, "A Phase 3, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus" and the "Preliminary Report: Month 36 Safety and Efficacy Data for Studies FVF4168g and FVF4170g" together demonstrate safety and efficacy of the ranibizumab 0.3-mg injection in the treatment of diabetic retinopathy in patients with diabetic macular edema.

The submitted analyses demonstrate that patients who were treated with intravitreal ranibizumab 0.3-mg every four weeks (approximately 28 days) experienced a greater than or equal to 3-step improvement based on the ETDRS Diabetic Retinopathy Severity Scale when compared to sham treatment.

Clinical, Biostatistics, Clinical Pharmacology, Pharmacology/Toxicology, Division of Monoclonal Antibodies, and OC/OMPQ/DGMPA/BMAB, and have recommended approval for this application.

Appendix 1

BLA 125156 for Lucentis (ranibizumab injection), Supplement 106, is recommended for approval for the treatment of diabetic retinopathy in patients with diabetic macular edema with the package insert labeling submitted by Genetech, Inc., on 2/05/2015

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
02/06/2015
For William Boyd

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA 125156
Submission Number	106
Submission Code	Supplement
Letter Date	August 7, 2014
Stamp Date	August 7, 2014
PDUFA Goal Date	February 6, 2015
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	December 31, 2014
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	Strength: Amount per 10 mg/mL Vial	Function	Reference to Standard or Specification
Ranibizumab	10 mg [a] 6 mg [b]	(b) (4)	Active ingredient	STN: BL 125156
α, α-trehalose dehydrate	(b) (4)			
L-histidine HCl monohydrate	(b) (4)			Ph. Eur.
L-histidine	(b) (4)			USP and Ph. Eur.
Polysorbate 20	(b) (4)		t	NF and Ph. Eur.
Water for Injection	(b) (4)			USP and Ph. Eur.

a Target fill volume for 0.5 mg
b Target fill volume for 0.3 mg

Dosing Regimen

Lucentis 0.3 mg (0.05 mL) is to be administered by intravitreal injection once a month (approximately 28 days).

(b) (4) .

Intended Population

Adults with diabetic retinopathy and diabetic macular edema.

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

1.2 Risk Benefit Assessment

The 24-Month Clinical Study Reports for Studies FVF4168g and FVF4170g, “A Phase 3, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects with Clinically Significant

Macular Edema with Center Involvement Secondary to Diabetes Mellitus" and the "Month 36 Safety and Efficacy Data for Studies FVF4168g and FVF4170g," were resubmitted within this Supplemental BLA 125156. Post hoc analyses of these studies demonstrate safety and efficacy of ranibizumab 0.3-mg injection in the treatment of patients with diabetic retinopathy. The two Phase 3 studies demonstrate replicative results in the ability of intravitreal ranibizumab when given every four weeks (approximately every 28 days) to improve diabetic retinopathy based on the ETDRS diabetic retinopathy severity scale (DRSS) compared to sham treatment. These trials included a sham treatment arm.
The submitted analyses demonstrate that patients who were treated with intravitreal ranibizumab 0.3-mg every four weeks (approximately 28 days) experienced a greater than or equal to 3-step improvement based on the ETDRS Diabetic Retinopathy Severity Scale when compared to sham treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

There are no postmarket requirements or commitments for this supplement.

2 Introduction and Regulatory 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), 0.5 mg 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.

Reference is also made to the Supplemental BLA for Lucentis (ranibizumab injection), 0.5 mg approved on June 22, 2010, for the treatment of patients with macular edema following retinal vein occlusion.

Reference is also made to the Supplemental BLA for Lucentis (ranibizumab injection), 0.3 mg approved on August 10, 2012, for the treatment of patients with diabetic macular edema.

In this supplemental BLA, Genentech seeks to update the Lucentis labeling with a new indication, (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

(b) (4)

Currently, the management of DR consists of:

- Systemic approaches during the early stages of DR. They include optimal control of hyperglycemia, hyperlipidemia, and hypertension.
- Surgical approaches for the advanced stages of DR. They include pan-retinal photocoagulation (PRP) and vitreous surgery.

The existing therapies for DR (e.g., metabolic control, PRP and vitreous surgery for the advanced stages of DR) either only work to slow down the worsening of DR or have serious side effects such as surgical complications or substantially reduced visual function due to laser scarring. A treatment that results in a robust DR improvement, and thus reverses DR worsening associated with subsequent vision loss, would represent a major advance in the management of DR. Therefore, there is a need for therapies that directly target the underlying disease mechanism, potentially working to not only slow down the worsening of DR but also provide patients with a clinically meaningful improvement in their underlying DR.

2.3 Availability of Proposed Active Ingredient in the United States

Ranibizumab injection 0.5-mg is currently marketed by the applicant as Lucentis (ranibizumab injection) for the treatment of neovascular (wet) age-related macular degeneration and the treatment of macular edema secondary to retinal vein occlusion.

Ranibizumab injection 0.3-mg is currently marketed by the applicant Lucentis (ranibizumab injection) for the treatment of diabetic macular edema.

2.4 Important Safety Issues With Consideration to Related Drugs

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 Summary of Presubmission Regulatory Activity Related to Submission

August 10, 2012 – Supplement 076 Approval. Lucentis (ranibizumab injection) 0.3 mg was approved for the treatment of patients with diabetic macular edema (DME).

May 20, 2014 – A Type-B, pre- sBLA meeting was scheduled to discuss the acceptability of the retinopathy data from Studies FVF4168g and FVF4170g (b) (4) . In preliminary responses, the Division agreed that the proposed efficacy and safety data from the studies appeared to be adequate to support the filing of a sBLA for (b) (4) . The Division also agreed with the proposed Statistical Analysis Plan for the Integrated Summary of Efficacy. Genentech was satisfied with the responses and cancelled the meeting.

July 17, 2014 – Genentech submitted an initial Pediatric Study Plan (PSP) to IND 8633 within 60 days of the planned pre-sBLA meeting.

2.6 Other Relevant Background Information

Diabetic retinopathy (DR) may occur at any time during the disease course as a complication of both Type 1 and Type 2 diabetes mellitus. The earliest manifestation of the disease, early non-proliferative diabetic retinopathy (NPDR), is characterized by microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts (called cotton wool spots), and, in more severe cases, venous beading and intraretinal microvascular abnormalities which are visualized on ophthalmoscopic examination or retinal photography. NPDR may progress to proliferative diabetic retinopathy (PDR) usually over a period of years and is characterized by growth of new, abnormal blood vessels (neovascularization) in the retina, optic disc, iris, and anterior chamber angle as a result of retinal ocular ischemia and the resultant increase in VEGF levels. The progression through NPDR and PDR is serious and represents clinically significant progression of the disease pathology to the advanced stages of the disease. PDR traditionally has been treated with laser intervention with panretinal photocoagulation (PRP) or surgical intervention with vitrectomy.

Studies FVF4168 g and FVF4170g enrolled patients with diabetic macular edema which is the leading cause of vision loss in diabetic retinopathy (DR) patients. All enrolled patients had both diabetic retinopathy and diabetic macular edema. Because DME may occur in early or advanced DR, the patient populations enrolled in Studies FVF4168g and FVF4170g included a range of retinopathy severity levels.

Progression of DR is measured in discrete steps as described by the ETDRS DR Severity Scale[1]. This scale is well established for objective quantification of retinopathy severity and a validated method for quantification of DR change. The DR anatomic

1 Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study Design and Baseline Patient Characteristics. ETDRS Study Report 7. Ophthamology 1991; 98:741-756.

worsening measured on the ETDRS scale has been shown to be associated with a clinically significant increase in the risk of visual loss.[2]

While Studies FVF4168g and FVF4170g were designed to evaluate the effects of ranibizumab on outcome measures associated with DME (e.g., changes over time in best corrected visual acuity [BCVA]), they also followed the improvement or worsening of the underlying DR symptoms on the ETDRS DR severity scale based on fundus photographs that were obtained at pre-specified time points and evaluated by an independent reading center. Evaluators of DR severity were masked to treatment assignment and all photographs were evaluated according to protocol specific criteria.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission contains post hoc analyses of data from Studies FVF4168g and FVF4170g originally submitted in S-076 which was approved August 10, 2012. Clinical site inspections were performed during the review of S-076.

There was no evidence that these studies were not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

This submission contains post hoc analyses of data from Studies FVF4168g and FVF4170g originally submitted in S-076 which was approved August 10, 2012. Clinical site inspections were performed during the review of S-076 and found to be adequate.

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.

2 The Diabetic Retinopathy Study Research Group. Four Risk Factors for Severe Visual Loss in Diabetic Retinopathy. The Third Report from the Diabetic Retinopathy Study. Arch Ophthalmol 1979; 97:654-655.

3.3 Financial Disclosures

This submission contains post hoc analyses of data from Studies FVF4168g and FVF4170g originally submitted in S-076 which was approved August 10, 2012. Genentech provided adequate financial disclosure information for Studies FVF4168g and FVF4170g during the review of S-076 approved August 10, 2012.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This supplemental BLA does not include any changes to the CMC information for this product.

4.2 Clinical Microbiology

This supplemental BLA does not include any changes to the Clinical Microbiology information for this product.

4.3 Preclinical Pharmacology/Toxicology

This supplemental BLA does not include any changes to the Preclinical Pharmacology/Toxicology information for this product.

4.4 Clinical Pharmacology

This supplemental BLA does not include any changes to the Clinical Pharmacology information for this product.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This supplemental BLA references the clinical study reports of the 24- and 36-month results of Study FVF4168g and FVF4170g.

Study	Design (Sites)	Population	Control	No. of Subjects Enrolled	Treatment Frequency and Duration	Dose(s)
FVF4168g (RIDE)	Multicenter, randomized, double-masked. Sham-controlled Months 1-24; Masked, Months 25-36; Open-label extension, up to Month 60. US and Latin America	Subjects with CSME-CI secondary to DM	Sham injection for 24 months	382	Ranibizumab arms: intravitreal injxns of 0.3 mg or 0.5 mg of ranibizumab q month during 36-month tx period. Sham arm: sham injxns q month for 25 months, after which subjects have the option to cross over to receive 0.5 mg ranibizumab at Month 25 (or earlier, if early treatment crossover criteria are met) for the remainder of the masked treatment period	0.3 mg (n=125) 0.5 mg (n=127) sham injxn (n=130)
FVF4170g (RISE)				377		0.3 mg (n=125) 0.5 mg (n=125) sham injxn (n=127)

CSME-CI = clinically significant macular edema with center involvement; DM = diabetes mellitus

5.2 Review Strategy

The two Phase 3 clinical trials FVF4168g and FVF4170g which were designed to evaluate the treatment of diabetic macular edema indication were reviewed in S-076 which was approved on August 10, 2012. These studies are referenced in this supplemental BLA 106 (b) (4)

Studies FVF4168 g and FVF4170g, enrolled patients with diabetic macular edema, a retinal condition which is the leading cause of vision loss in patients with DR.[3] All of the patients enrolled in these studies had DR and DME. While the patients were followed for changes in diabetic macular edema, they were also evaluated for changes to their underlying DR.

Progression of DR on fundus photography is measured in discrete steps on the ETDRS DR Severity Scale. This scale is described in a publication of the Early Treatment in Diabetic Retinopathy Study Group in 1991.[4] The DR anatomic worsening measured on the ETDRS scale has been shown to be associated with a clinically significant increase in the risk of visual loss.

The additional analyses of Studies FVF4168g and FVF4170g (b) (4) are reviewed here.

3 Johnson, MW. Etiology and Treatment of Macular Edema. Am J Ophthalmol 2009; 147:11-21.
4 Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study Design and Baseline Patient Characteristics. ETDRS Study Report 7. Ophthamology 1991; 98:741-756.

5.3 Discussion of Individual Studies/Clinical Trials

Studies FVF4168g and FVF4170g: A Phase 3, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus

Reviewer's Comment:
The clinical development plan for the (b) (4) *included two studies, FVF4168g and FVF4170g, submitted in this Supplement. The studies are identical in design and were conducted in parallel. There were no differences in population studied, inclusion and exclusion criteria, planned treatment groups, treatment schedules, study assessments, efficacy endpoints, or statistical analysis methods.*

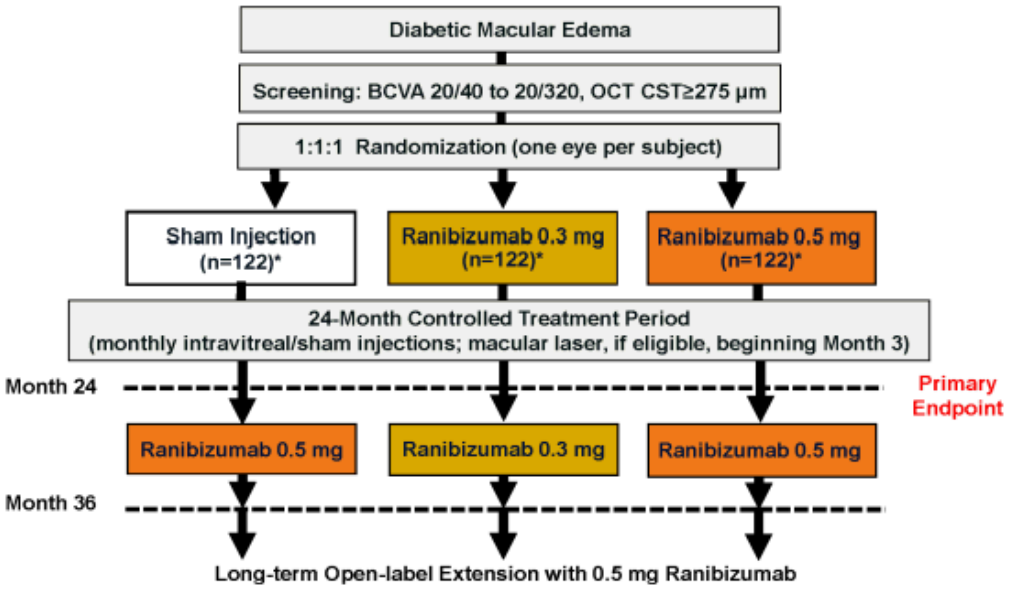
Both studies were reviewed in S-076 for the treatment of diabetic macular edema which was approved on August 10, 2012. These studies are relevant for both indications because patients with diabetic macular edema have diabetic retinopathy by definition; diabetic retinopathy is the broader diagnostic term.

Overall Study Design
Each of the trials was a double-masked, multicenter, randomized, sham-injection-controlled study of the efficacy and safety of ranibizumab injection in subjects with clinically significant macular edema with center involvement (CSME-CI) secondary to diabetes mellitus (Type 1 or 2). The duration of the controlled and masked period of the study was 24 months, excluding the screening period.

Starting at Month 25 visit, and for the remainder of their treatment period, subjects randomized to the sham arm who had not discontinued from study treatment could elect to cross over and receive monthly injections of 0.5-mg ranibizumab for the next 12 months. Thus, only the first 24 months of the 36-month masked period were sham-controlled.

Additionally, the protocol was amended to include an open-label extension period for subjects who were in the trial at Month 36. This open-label extension (OLE) is up to 24 additional months beyond Month 36.

Figure 1 FVF4168g and FVF4170g Study Design



* Target enrollment.

Eligible subjects were to be randomized in a 1:1:1 ratio so that approximately 122 subjects would receive 0.5-mg ranibizumab, approximately 122 would receive 0.3-mg ranibizumab, and approximately 122 will receive sham injection. The randomization was stratified by three baseline factors:

- VA (≤ 55, > 55 letters) in the study eye based on the Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA assessment
- HbA_{1c} (≤ 8%, > 8%)
- Prior therapy for DME in the study eye (yes or no)

Only the study eye would receive intravitreal injections of ranibizumab or sham injections. The non–study eye would receive laser photocoagulation for CSME consistent with the standard of care.

Ranibizumab and Sham Treatment

Two doses of ranibizumab (0.5-mg and 0.3-mg) were used in the studies. Ranibizumab was administered intravitreally to subjects in a single-dose regimen every month during the 36-month treatment period. Missed injection doses were not replaced. Details of the pre-injection procedures, ranibizumab administration and post-injection procedures were provided within the protocol.

Sham intravitreal injections were administered to subjects according to the same dosing schedule as ranibizumab injections. The sham intravitreal injection procedure mimicked an intravitreal injection except that the blunt end of an empty syringe was pressed

against an anesthetized eye instead of a needle attached to a ranibizumab-filled syringe. The sham was an empty, sterile, 3-cc stoppered glass vial.

Focal Laser Rescue Treatment

Macular laser photocoagulation for CSME-CI was offered as rescue treatment to all subjects starting at Month 3. Treatment was focal laser for rescue therapy, using the laser and contact lens of the investigator's choice, provided that there is sufficient room to apply laser burns safely. Subjects were treated with laser photocoagulation no less than 3 months apart consistent with the usual standard of care (ETDRS Research Group 1985).

Rescue laser treatment was indicated if all of the following criteria were met:

- The evaluating physician deems such therapy to be beneficial.
- The subject's central foveal thickness (CFT) is ≥250 µm with $<$ 50 µm reduction from the prior month's measurement.
- The subject has not received laser in the past 3 months.

Open Label Extension (OLE) Period

All subjects who did not discontinue study treatment early and completed the Month 36 Visit were eligible to enter the open-label extension phase which lasted up to Month 60. During the open-label phase, intravitreal injections of 0.5-mg ranibizumab were administered (no more than monthly) when the patient's study eye met either of the following criteria:

- Evidence of DME on optical coherence tomography (OCT) (e.g., presence of intraretinal fluid or cysts, subretinal fluid, or subretinal pigment epithelial fluid) due to DME and not another cause.
- The patient's vision has worsened by ≥ 5 letters compared with the Month 36 visit, due to DME and not another cause.

If a patient was treated at any visit during the OLE phase, the next scheduled visit occurred approximately 30 days after the treatment visit. If a patient was not treated, the interval between scheduled study visits could be extended to approximately 60 days or a maximum of approximately 90 days.

The 24-month and 36-month data for Studies FVF4168g and FVF4170g were reviewed previously prior to the approval of Supplement 076 (S-076). Please refer to S-076 Clinical review for further study details.

Table 5.3-3
Masked Phase Study Flowchart: Screening, Treatment Period Day 0 through Month 14, and Early Termination

Assessment	Screen.	Day		Month													Early
		0	7	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Term. [a]
Window (Days)	Days –28 to –1	NA	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+30 (± 7)
Written informed consent(s)	x																	
Review of inclusion and exclusion criteria	x	x																
RetDQoL questionnaire [b]		x							x						x			x
NEI VFQ-25 [b]		x							x						x			x
Date of first CSME-CI diagnosis	x																	
Medical and surgical history [c]	x																	
Demographic data	x																	
Physical examination	x														x			x
Vital signs [d]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height (screening only) and weight	x																	x
Central laboratory samples (hematology, coagulation panel, serum chemistry, & urinalysis) [e]	x								x						x			x
Serum anti-ranibizumab antibody sample [e]	x														x			x

Table 5.3-3
Masked Phase Study Flowchart: Screening, Treatment Period Day 0 through Month 14, and Early Termination (continued)

Assessment	Screen.	Day		Month													Early
		0	7	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Term. [a]
Window (Days)	Days –28 to –1	NA	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+30 (± 7)
Serum PK sample [e] for ranibizumab concentration	x				x [f]										x			x
Optional serum PK sample [e] for ranibizumab concentration			x [g]		x [g]													
Optional plasma sample [e, h]	x								x						x			x
Optional aqueous humor sample [e, i]		x							x						x			x
Serum pregnancy test [e, j]	x																	x
Urine pregnancy test [e, j]									x						x			
BCVA testing (4 m) [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reading speed assessment for subjects who read English [k]		x							x						x			x
Contrast sensitivity [k]		x							x						x			x
Intraocular pressure [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Slitlamp examination [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 5.3-3
Masked Phase Study Flowchart: Screening, Treatment Period Day 0 through Month 14, and Early Termination (continued)

Assessment	Screen.	Day		Month													Early
		0	7	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Term. [a]
Window (Days)	Days –28 to –1	NA	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+30 (± 7)
OCT [m, n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography [m, n]	x					x			x						x			x
Fluorescein angiography [m, n]	x					x			x						x			x
Site to contact IVRS [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assessment for macular laser therapy [p]						Per rescue laser treatment criteria, assess at every visit starting at the Month 3 visit.												
Administration of ranibizumab or sham injection (study eye)		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Post-injection finger counting and IOP measurement [q]		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	x	x
Adverse events [s]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [t]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact [u]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	

BCVA=best corrected visual acuity; CSME-CI=clinically significant macular edema with center involvement; NA=not applicable; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; IOP=intraocular pressure; IVRS=interactive voice response system; OCT=optical coherence tomography; PK=pharmacokinetic; RetDQoL=Retinopathy Dependent Quality of Life.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening.

Table 5.3-3
Masked Phase Study Flowchart: Screening, Treatment Period Day 0 through Month 14, and Early Termination (continued)

[a] For subjects who withdraw early from the study, perform 30 (±7) days following the last injection of study treatment.

[b] The NEI VFQ-25 questionnaire should be administered by designated masked site personnel prior to a subject completing any other study procedures.
Note: Do not administer the RetDQoL questionnaire to study subjects after the site's IRB approval of protocol amendment 3, dated 17 September 2009. The questionnaire is being withdrawn by Genentech.

[c] Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, and ophthalmic history) and tobacco and alcohol use.

[d] Vital signs consist of blood pressure, respiration, pulse, and temperature; on days of study drug administration, perform pre-injection.

[e] Obtain pre-injection (and prior to fluorescein angiography [if applicable)] except at screening, Month 36, or early termination (no time requirement). Subjects should fast for the laboratory sample collection at the screening visit only.

[f] Collect serum PK sample from all subjects 7 (+3) days after the third dosing and serum antibody and serum PK samples at the screening and Month 12 visit, or early termination visit (if applicable).

[g] Collect serum PK sample (at U.S. sites only) from subjects who consent to provide the serum PK samples and sign the Research Informed Consent Form prior to the current amendment (A2) at the Day 7 (±2 days) visit as well as 3 days (±2 days) and 14 days (±2 days) after the third dose of study drug and then again at the next scheduled visit prior to study treatment. In the event that a subject misses the PK draws after the third study dose, the subject may have the serum samples drawn after the fourth, fifth, or sixth dose. Subjects must complete the PK sampling within a given monthly dosing interval. Note: after the site's IRB has approved current protocol version (A2), there will be no further collection of the optional serum samples from the additional/new subjects.

[h] Collect plasma sample (at U.S. sites only) from subjects who consent to provide the plasma samples and sign the Research Informed Consent Form at screening and prior to dosing (if applicable) at the Month 6 and 12 visits, or early termination visit.

[i] At selected U.S. sites only, obtain aqueous humor sample prior to dosing (if applicable) at the Day 0, and Month 6 and 12 visits, or early termination visit for subjects who consent to provide the aqueous humor samples and sign the Research Informed Consent Form.

[j] For women of childbearing potential. At screening, obtain serum (β-human chorionic gonadotropin) sample; at all other visits, perform a urine pregnancy test at the clinic.

[k] Perform prior to dilating eyes and pre-injection (when applicable). The reading speed assessment is performed at U.S. sites only.

[l] Obtain prior to dilating eyes, pre-injection for both eyes.

[m] Perform pre-injection.

[n] The central reading center (the University of Wisconsin Fundus Photograph Reading Center [UWFPRC]) will grade OCT images for determination of a subject's eligibility at screening. At all other visits, OCT images (study eye only), fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the UWFPRC for grading and/or storage.

Table 5.3-3
Masked Phase Study Flowchart: Screening, Treatment Period Day 0 through Month 14, and early Termination (continued)

[o] At screening, site personnel are to telephone interactive voice response system (IVRS) to obtain subject screening number prior to assessments; on Day 0, call IVRS for subject randomization number and study drug kit assignment after all assessments are performed; at the remaining scheduled study visits, obtain study drug kit assignment. At the early termination visit, contact the IVRS to request subject's status be changed to "early termination."

[p] Subjects who have not discontinued study treatment may be eligible to receive macular rescue laser photocoagulation therapy (focal/grid) starting at the Month 3 visit, based on rescue criteria given in Section 3.1.5 and provided that there is sufficient room to apply laser burns safely.

[q] Finger counting test, followed by hand motion and light perception tests (when necessary) will be performed by the unmasked treating investigator only within 15 minutes post-injection. IOP measurement will be obtained 60 (±10) minutes post-injection (when applicable) for the study eye only by masked site personnel only; the method used for a subject must remain consistent throughout the study.

[r] Record any concomitant medications used by the subject within 7 days preceding Day 0 (i.e., any prescription medications 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 will be recorded starting on Day 0 through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab should be followed until event resolves or the event is assessed as irreversible, chronic, or stable, even if subject's participation in the study is over.

[t] Record all concurrent ocular procedures performed on the study or fellow eye.

[u] After Day 0, subjects will be contacted 3 (± 1) days following study treatment to elicit reports of any decreases in vision, occurrence of eye pain, unusual redness, or any other new ocular symptoms. Subjects will also be asked whether they have taken the prescribed, self-administered, post-injection antimicrobials.

Table 5.3-3
Masked Phase Study Flowchart: Month 15 through Month 24, and Early Termination

Assessment or Procedure	Treatment Period (Month)										Early Term. [a]
	15	16	17	18	19	20	21	22	23	24	
Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+30 (±7)
RetDQoL questionnaire [b]				x						x	x
NEI VFQ-25 [b]				x						x	x
Physical examination										x	x
Vital signs [c]	x	x	x	x	x	x	x	x	x	x	x
Central laboratory samples (hematology, coagulation panel, serum chemistry, and urinalysis) [d]				x						x	x
Serum anti-ranibizumab antibody sample [d]										x	x
Serum PK sample for ranibizumab concentration [d]										x	x
Optional plasma sample [d, e]				x						x	
Urine pregnancy test [d, f]				x						x	x
Optional aqueous humor sample [d]											x
BCVA testing (4 m) [g]	x	x	x	x	x	x	x	x	x	x	x
Reading speed assessment (for subjects who read English) [g]										x	x
Contrast sensitivity [g]										x	x
Intraocular pressure [h]	x	x	x	x	x	x	x	x	x	x	x
Slitlamp examination [i]	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy [i]	x	x	x	x	x	x	x	x	x	x	x

Table 5.3-3
Masked Phase Study Flowchart: Month 15 through Month 24, and Early Termination (continued)

Assessment or Procedure	Treatment Period (Month)										Early Term. [a]
	15	16	17	18	19	20	21	22	23	24	
Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+30 (± 7)
Fluorescein angiography [i, j]				x						x	x
OCT [i, j]	x	x	x	x	x	x	x	x	x	x	x
Fundus photography [i, j]				x						x	x
Assessment for macular laser therapy [k]	Per macular rescue laser treatment criteria, assess at every visit.										
Site personnel to telephone IVRS [l]	x	x	x	x	x	x	x	x	x	x	x
Administration of ranibizumab or sham injection (study eye)	x	x	x	x	x	x	x	x	x	x	
Post-injection finger counting and IOP measurement [m]	x	x	x	x	x	x	x	x	x	x	
Concomitant medications [n]	x	x	x	x	x	x	x	x	x	x	x
Adverse events [o]	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [p]	x	x	x	x	x	x	x	x	x	x	x
Follow-up contact [q]	x	x	x	x	x	x	x	x	x	x	

Source: Appendix A-2 in Protocol FVF4168g.

BCVA=best corrected visual acuity; NA=not applicable; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; IVRS=interactive voice response system; OCT=optical coherence tomography; PK=pharmacokinetic; RetDQoL=Retinopathy Dependent Quality of Life.

Note: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening.

[a] For subjects who withdraw early from the study, perform 30 (±7) days following the last injection of study treatment or the last study visit.

Table 5.3-3
Masked Phase Study Flowchart: Month 15 through Month 24, and Early Termination (continued)

[b] The NEI VFQ-25 should be administered by designated masked site personnel prior to a subject completing any other study procedures. Note: Do not administer the RetDQoL questionnaire to study subjects after the site's IRB approval of protocol amendment 3, dated 17 September 2009. The questionnaire is being withdrawn by Genentech.

[c] Vital signs consist of blood pressure, respiration, pulse, and temperature; on days of study drug administration, perform pre-injection.

[d] Obtain pre-injection (and prior to fluorescein angiography [if applicable)] except early termination (no time requirement). Subjects should fast for the laboratory sample collection at the screening visit only.

[e] Collect plasma sample (at U.S. sites only) from subjects who consent to provide plasma samples and sign the Research Informed Consent Form prior to dosing (if applicable) at the Month 18 and Month 24 visits, or early termination visit.

[f] For women of childbearing potential, perform the urine pregnancy test at the clinic.

[g] Perform prior to dilating eyes and pre-injection (when applicable). The reading speed is performed at U.S. sites only.

[h] Obtain prior to dilating eyes, pre-injection for both eyes and 60 (±10) minutes post-injection (when applicable) for study eye only.

[i] Perform pre-injection.

[j] OCT images (study eye only), fluorescein angiograms, and fundus photographs will be forwarded to the UWFPRC for grading and/or storage.

[k] Subjects who have not discontinued study treatment may be eligible to receive macular rescue laser therapy (focal/grid) starting at the Month 3 visit, based on rescue criteria given in Section 3.1.5 and provided that there is sufficient room to apply laser burns safely.

[l] At scheduled visits, obtain study drug kit assignment. At the early termination visit, contact the IVRS to request subject's status be changed to "early termination."

[m] Finger counting test, followed by hand motion and light perception tests (when necessary) will be performed by the unmasked treating investigator only within 15 minutes post-injection. IOP measurement will be obtained 60 (±10) minutes post-injection (when applicable) for the study eye only by masked site personnel only; the method used for a subject must remain consistent throughout the study.

[n] Record any concomitant medications used by the subject (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications and pre-injection and post-injection medications [e.g., proparacaine, anti-microbials, etc.]).

[o] Adverse events will be recorded starting on Day 0 through the last study visit. Adverse events assessed by the evaluating physician as related to ranibizumab should be followed until event resolves or the event is assessed as irreversible, chronic, or stable, even if subject's participation in the study is over.

[p] Record all concurrent ocular procedures performed on the study or fellow eye.

[q] Subjects will be contacted 3 (±1) days following study treatment to elicit reports of any decreases in vision, occurrence of eye pain, unusual redness, or any other new ocular symptoms. Subjects will also be asked whether they have taken the prescribed, self-administered, post-injection antimicrobials.

Table 5.3-3
Study Flowchart: Safety Assessment Visit

Assessment [a]	Day 0–Month 35 [d]
Best corrected visual acuity testing (4 m) [b]	x
Intraocular pressure measurement [c]	x
Vital signs (blood pressure, respiration, pulse, and temperature)	x
Slitlamp examination	x
Dilated binocular indirect high-magnification ophthalmoscopy	x
Concomitant medications	x
Concurrent ocular procedures	x
Adverse events	x

Notes: All ocular assessments should be performed on both eyes by the designated evaluating investigator and masked site personnel.

It is not the purpose of the safety assessment visit to provide study eye treatment with Genentech-provided study drug.

[a] If determined to be necessary by the evaluating physician, perform assessments following the 3-day (±1 day) post-injection telephone call.

[b] Perform finger counting test followed by hand motion and light perception tests, when necessary.

[c] The method used for the IOP measurement for a subject must remain consistent throughout the study.

[d] If the subject continues to the open-label extension period of the study (see Appendix R) the safety assessment visit can be conducted between the scheduled Months 36 and 59 study visits.

Statistical Analysis Plan (b) (4)

Diabetic Retinopathy Outcome Measures
The main analysis was based on Month 24 data since this was the sham-controlled study period. The Month 36 analysis serves as supportive analysis because sham subjects crossed over to receive 0.5-mg ranibizumab after Month 24 and pure sham-controlled data was no longer available.

Main Efficacy Outcome Measure
Proportion of subjects with a 3-step or greater improvement from baseline in the ETDRS diabetic retinopathy severity level at Month 24, as assessed by the central reading center using fundus photography (FP).

Supportive Efficacy Outcome Measures

- Proportion of subjects with a ≥ 3-step improvement from baseline in the ETDRS DR severity score at 36 months, as assessed by the central reading center using FP.
- Proportion of subjects with a ≥ 2-step improvement from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP.
- Proportion of subjects with a ≥ 3-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP.
- Proportion of subjects with a ≥ 2-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP.
- Proportion of subjects progressing to PDR as determined by the indirect ophthalmoscopy assessment of the presence of neovascularization on the optic disc, elsewhere on the retina, or iris by Month 24 and 36.
- Time to first new PDR event, where a new PDR event was defined by (1) progression from NPDR (DR severity score < 60) at baseline to PDR (DR severity score ≥ 60) at a later timepoint, (2) use of PRP laser treatment, (3) vitreous hemorrhage (AE or slit lamp grade 0 at baseline to > 0 at a later timepoint), (4) cases identified by ophthalmoscopy as described above, (5) use of vitrectomy for reasons related to DR or its complications, (6) iris neovascularization AE, or (7) retinal neovascularization AE, whichever occurred first. Subjects with a baseline DR severity score ≥ 60, were considered as having experienced a new PDR event if any one of the conditions as described in (2) to (7) occurred.

Reviewer's Comment:
The 'Time to first new PDR event' supportive endpoint has not been used because its clinical relevance is dependent on the baseline retinopathy level.

Statistical Methods

For the Month 24 and Month 36 analyses, the screening evaluation served as baseline for the FP outcome measure. The Day 0 evaluation will serve as baseline for slit-lamp examination and indirect ophthalmoscopy. If the screening or Day 0 value designated as baseline for an assessment is missing for a subject, the latest pretreatment value (i.e., measured on or prior to Day 0) served as baseline for that subject.

FP outcome measures were based on assessment by the central reading center. Analyses of FP outcome measures were performed for the study eye only. Unless otherwise specified, all statistical tests are two-sided. Descriptive summaries include the mean, standard deviation, median, and range for continuous variables, and counts and percentages for categorical variables.

Analysis Populations

Unless otherwise specified, randomized subjects (intent-to-treat [ITT] population) will be used for DR-related efficacy analyses. The ITT population includes subjects randomized in the studies, whether treatment was received or not. Treatment groups for this population were defined according to the treatment assignment at randomization.

Efficacy Analyses

Analyses of the main and supportive endpoints include all randomized subjects (the ITT population). Subjects were analyzed according to their randomized treatment assignment. Missing data were imputed using the last observation carried forward (LOCF) method for the main and supportive endpoint related to change of DR severity scale from FP.

The analyses of endpoints for the Month 36 analysis include all data collected during the Month 36 study period when treatment assignment was masked, including those collected after the initiation of ranibizumab treatment in subjects in the sham-injection group who participated in the ranibizumab treatment crossover plan.

Comparisons of efficacy were performed separately for each ranibizumab dose group and the sham-injection (control) group (or the sham/0.5-mg crossover group after Month 24). All pairwise comparisons for assessing treatment difference include only two treatment groups (one ranibizumab arm vs. control) at a time.

Unless otherwise noted, the statistical tests for efficacy analyses were stratified by baseline BCVA (≤ 55, >55 letters), HbA_{1c} (≤8%, >8%), and prior therapy for DME (yes, no) with values based on the CRF and central laboratory data.

In addition to p-values for statistical tests, the point estimates and confidence intervals (CIs) were provided for the proportion (for binary variables) or mean (for continuous 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. For unstratified analyses of proportions, the proportion for each treatment group and the overall difference in proportions between treatment groups were estimated using the observed proportions and the difference in the observed proportions. For stratified analyses of proportions, the

proportion for each treatment group and the overall difference in proportions between treatment groups were estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata using the Cochran-Mantel-Haenszel (CMH) weights. The stratification variables were the same as those used in the stratified test for treatment difference. CIs of the proportion for each treatment group and the overall difference in proportions between treatment groups (unstratified or stratified) will be calculated using the normal approximation to the binomial distribution.

The analyses of time to diabetic retinopathy progression (TTDRP) will be based on data collected up to Month 36. TTDRP will be calculated as time from date of randomization to the date of the first occurrence of DR progression. For subjects without any post-baseline assessment, the TTDRP will be censored at Day 1. For subjects who have not experienced any DR progression event as of Month 36, the TTDRP will be censored at the date of their last evaluation. For subjects who were originally randomized to sham and participated in the crossover plan at Month 24, the TTDRP will not be censored at the time of crossover to 0.5-mg ranibizumab.

Each ranibizumab group will be compared against the sham control group using the log rank test, stratified by baseline BCVA, HbA_{1c}, and prior therapy for DME. Kaplan-Meier curves will also be generated for each treatment group.

Type I Error Management Plan
Except for the proportion of subjects with a 3-step or greater progression from baseline in the ETDRS diabetic retinopathy severity level as assessed by the central reading center using FP as pre-specified in the original study protocol all analyses are exploratory in nature. Family-wise type I error is not strongly controlled among the DR-related analyses.

Sensitivity Analyses
Different methods of handling missing data will be used for the sensitivity analyses. For main and supportive endpoints from FP, sensitivity analysis based on observed data will be performed.

Missing Data
Missing data for the main and supportive efficacy endpoints from FP will be imputed using the LOCF method unless specified otherwise. Sensitivity analyses will be performed using observed data without imputation.

Subjects with missing values for baseline variables required in the analysis of an efficacy endpoint, either as covariates in model-based analyses or for calculating the change from baseline, will be excluded from the analysis of that endpoint. Missing data on baseline strata for BCVA, HbA_{1c}, and prior therapy for DME based on CRF and central laboratory data required in the stratified analyses as stratification variables will be imputed using data entered into the IVRS at randomization.

Subjects without any post-baseline assessment of indirect ophthalmoscopy to determine progression to PDR (e.g., those who discontinued from the study or were lost to follow-up

without any post-randomization visit) will be considered as not progressing to PDR in the analysis of the proportion of subjects progressing to PDR.

For time to DR progression analysis, TTDRP will be censored at the last assessment available if a subject does not experience a DR progression event as of the clinical data cutoff at Month 36, or Day 1 if there is no post-baseline assessment for the subject.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

This supplemental BLA presents a post hoc analysis of data from Phase 3 studies FVF4168g and FVF4170g to support revision of the Lucentis package insert (b) (4) . Except for the proportion of subjects with a 3-step or greater progression from baseline in the ETDRS Diabetic Retinopathy Severity level as assessed by the central reading center using FP which was pre-specified in the original study protocol, all analyses are exploratory in nature. Family-wise type I error is not strongly controlled among the DR-related analyses.

The 24-month data from Phase 3 studies FVF4168g and FVF4170g were submitted on October 10, 2011 in support of the safety and efficacy of Lucentis (ranibizumab injection) for the treatment of diabetic macular edema. Both studies met their primary endpoints and were thoroughly reviewed in S-076 for the treatment of diabetic macular edema, approved in August 2012. The 60-month data for these studies was submitted in February 2014 and was reviewed in S-105, approved November 25, 2014.

6.1.1 Study FVF4168g (RIDE)

6.1.1.1 Methods

The 24-month controlled data and 36-month final data from the Phase 3 study, FVF4168g, was reviewed in Supplement 076 which was approved on August 10, 2012. The 60-month data from the open label extension study was reviewed in S-105.

Study FVF4168g data is referenced in this supplemental BLA (S-106) (b) (4)

6.1.1.2 Demographics

Table 6.1.1.2-1 Baseline Demographics and Characteristics

Demographic	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Age (yr)			
N	130	125	127
Mean (SD)	63.5 (10.8)	62.7 (11.1)	61.8 (10.1)
Range	22.0-91.0	24.0-88.0	29.0-84.0
Age group (yr)			
N	130	125	127
18 - <25	1 (0.8%)	1 (0.8%)	0
25 - <35	0	1 (0.8%)	2 (1.6%)
35 - <45	4 (3.1%)	5 (4.0%)	4 (3.1%)
45 - <55	19 (14.6%)	19 (15.2%)	19 (15.0%)
55 - <65	45 (34.6%)	44 (35.2%)	47 (37.0%)
65 - <75	42 (32.3%)	36 (28.8%)	45 (35.4%)
75 - <85	15 (11.5%)	18 (14.4%)	10 (7.9%)
85 - <95	4 (3.1%)	1 (0.8%)	0
≥ 95	0	0	0
Sex, n (%)			
N	130	125	127
Male	66 (50.8%)	73 (58.4%)	80 (63.0%)
Female	64 (49.2%)	52 (41.6%)	47 (37.0%)
Ethnicity, n (%)			
N	130	125	127
Hispanic or Latino	37 (28.5%)	33 (26.4%)	31 (24.4%)
Not Hispanic or Latino	93 (71.5%)	91 (72.8%)	93 (73.2%)
Not available	0	1 (0.8%)	3 (2.4%)
Race, n (%)			
N	130	125	127
American Indian or Alaska Native	1 (0.8%)	1 (0.8%)	2 (1.6%)
Asian	2 (1.5%)	5 (4.0%)	5 (3.9%)
Black or African American	15 (11.5%)	14 (11.2%)	13 (10.2%)
Native Hawaiian/Other Pacific Islander	0	1 (0.8%)	0
White	104 (80.0%)	99 (79.2%)	105 (82.7%)
Not available	8 (6.2%)	5 (4.0%)	2 (1.6%)
Duration of diabetes at randomization (yr)			

Demographic	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
N	122	119	124
Mean (SD)	16.6 (10.6)	16.0 (9.8)	15.3 (10.1)
Range	0.4 – 51.5	0.1 – 51.7	0.1 – 55.4
Glycosylated hemoglobin (HbA_{1c})			
N	125	120	123
Mean (SD)	7.6 (1.4)	7.6 (1.3)	7.6 (1.5)
Glycosylated hemoglobin (HbA_{1c}) group			
N	125	120	123
≤ 8	84 (67.2%)	79 (65.8%)	83 (67.5%)
> 8	31 (32.8%)	41 (34.2%)	40 (32.5%)
Diastolic blood pressure (mmHg)			
N	130	125	127
Mean (SD)	75.8(10.6)	78.7 (10.4)	78.0 (11.3)
Range	44.0 – 118.0	58.0 – 104.0	57.0 – 117.0

Reviewer's comment:
Approximately two-thirds of the patients enrolled were age 55-75 years with the mean age being 62 years. Randomization yielded more male subjects in the ranibizumab groups compared with the sham group.

In 30-40% of the subjects enrolled, diabetes was not under optimal glycemic control as measured by glycosylated hemoglobin (HgbA1c). The study excluded subjects with HgbA1c values greater than 12%. The American Diabetic Association recommends a value of ≤ 7% for non-pregnant adults.

Table 6.1.1.2-2
Baseline Ocular Characteristics in the Study Eye

Characteristic	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Visual acuity			
Number of letters (0-100)			
N	130	125	127
Mean (SD)	57.3 (11.2)	57.5 (11.6)	56.9 (11.8)
Range	25-77	20-78	15-73
Distribution, n (%)			
≤ 55	50 (38.5%)	50 (40.0%)	46 (36.2%)
> 55	80 (61.5%)	75 (60.0%)	81 (63.8%)
Approximate Snellen equivalent			

Characteristic	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
N	130	125	127
20/200 or worse	10 (7.7%)	9 (7.2%)	11 (8.7%)
Better than 20/200 to worse than 20/40	95 (73.1%)	92 (73.6%)	91 (71.7%)
20/40 or better	25 (19.2%)	24 (19.2%)	25 (19.7%)
Contrast sensitivity			
N	128	125	127
Mean (SD)	26.4 (5.9)	26.7 (5.5)	26.8 (5.1)
Range	10-46	10-35	11-40

Reviewer's Comment:
The treatment groups were well balanced regarding the baseline visual function characteristics.

Table 6.1.1.2-3
Baseline Fluorescein Angiography Characteristics in the Study Eye

Characteristic	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Total area of capillary loss in center, inner, and outer subfields, calculated (DA)			
N	116	106	107
Mean (SD)	0.183 (0.457)	0.265 (0.898)	0.327 (0.986)
Range	0.00-2.53	0.00-7.58	0.00-6.33
Total area of fluorescein leakage in center, inner and outer subfields, calculated (DA)			
N	127	120	123
Mean (SD)	8.392 (4.671)	9.052 (4.533)	8.402 (4.751)
Range	0.00-16.00	0.24-16.00	0.52-16.00
Total area of cystoid changes in center, inner, and outer subfields, calculated (DA)			
N	127	120	123
Mean (SD)	0.887 (1.154)	1.299 (1.826)	1.103 (1.700)
Range	0.00-6.36	0.00-10.96	0.00-8.47

Reviewer's Comment:
The treatment groups were well balanced regarding baseline study eye characteristics as assessed by fluorescein angiography.

Table 6.1.1.2-4
Baseline Fundus Photography Characteristics of the Study Eye

Characteristic	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Total area of retinal thickening in central, inner, and outer subfields (DA)			
N	122	115	121
Mean (SD)	8.423 (4.197)	8.355 (4.156)	7.988 (4.511)
Range	0.86-16.00	1.58-16.00	0.00-16.00
ETDRS diabetic retinopathy severity level			
N	128	124	126
1 – DR severity level 10, 12 (DR absent)	1 (0.8%)	0	1 (0.8%)
2 – DR severity level 14A-14C, 14Z, 15, 20 (DR questionable, microaneurysms only)	3 (2.3%)	1 (0.8%)	1 (0.8%)
3 – DR severity level 35A-35F (mild NPDR)	21 (16.4%)	20 (16.1%)	17 (13.5%)
4 – DR severity level 43A, 43B (moderate NPDR)	12 (9.4%)	13 (10.5%)	18 (14.3%)
5 – DR severity level 47A-47D (moderately severe NPDR)	38 (29.7%)	35 (28.2%)	28 (22.2%)
6 – DR severity level 53A-53E (severe NPDR)	6 (4.7%)	9 (7.3%)	6 (4.8%)
7 – DR severity level 60,61A, 61B (mild PDR)	32 (25.0%)	32 (25.8%)	38 (30.2%)
8 – DR severity level 65A-65C (moderate PDR)	9 (7.0%)	5 (4.0%)	8 (6.0%)
9 – DR severity level 71A- 71D (high risk PDR)	2 (1.6%)	2 (1.6%)	1 (0.8%)
10 – DR severity level 75 (high risk PDR)	0	0	1 (0.8%)
90 – DR severity level 90 (cannot grade)	4 (3.1%)	7 (5.6%)	7 (5.6%)

Reviewer's Comment:
Sixty-five to 68 percent of the patients randomized had moderately severe NPDR or worse (DR severity level ≥ 47). In the sham treatment group and ranibizumab 0.3-mg treatment groups, most patients had moderately severe NPDR (47), 29.7% and 28.2% respectively. In the ranibizumab 0.5-mg treatment group, the highest percentage of patients, 30.2%, had mild PDR (60, 61). One patient had high risk PDR (DR severity level 75) at baseline.

Less than 10 patients (6.2 – 7.2%) in each treatment group had no DR or questionable DR (DR severity level ≤ 20). The treatment groups were similarly balanced regarding the baseline study eye ETDRS diabetic retinopathy severity levels as assessed by fundus photography.

Table 6.1.1.2-5
Baseline Optical Coherence Tomography Characteristics of the Study Eye

Characteristic	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Central foveal thickness (µm)			
N	130	125	127
Mean (SD)	447.4 (154.4)	482.6 (149.3)	463.8 (175.5)
Median	438.0	465.0	434.0
Range	142-938	147-901	82-1241
Distribution, n (%)			
< 450	69 (53.1%)	57 (45.6%)	66 (52.0%)
≥ 450	61 (46.9%)	68 (54.4%)	61 (48.0%)
Central subfield thickness (µm)			
N	116	118	113
Mean (SD)	442.3 (124.9)	470.0 (126.6)	469.2 (154.4)
Median	422.5	436.5	432.0
Range	256-896	208-872	274-1209
Distribution, n (%)			
< 450	69 (59.5%)	62 (52.5%)	63 (55.8%)
≥ 450	47 (40.5%)	56 (47.5%)	50 (44.2%)
Total retinal volume (mm^3)			
N	112	115	106
Mean (SD)	9.4 (1.9)	9.5 (1.9)	9.7 (2.7)
Median	9.3	9.1	9.3
Range	6-17	6-14	6-24

a Central foveal thickness (CFT) was defined as the center point thickness.

Reviewer's Comment:
The baseline central foveal and subfield thicknesses were comparable across all treatment groups but slightly higher in ranibizumab groups.

Table 6.1.1.2-6
Diabetic Retinopathy History of the Study Eye

	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Non-proliferative diabetic retinopathy (NPDR)			
NPDR present			
N	130	125	127
Yes	117 (90.0%)	116 (92.8%)	112 (88.2%)
No	13 (10.0%)	9 (7.2%)	15 (11.8%)

	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Time from first known NPDR diagnosis to randomization (yr)			
N	117	114	112
Mean (SD)	3.0 (3.6)	2.5 (4.3)	2.5 (3.1)
Median	1.6	1.3	1.5
Range	0.0-18.6	0.0-40.5	0.0-15.7
Clinically significant macular edema (CSME)			
CSME present			
N	130	125	127
Yes	130 (100.0%)	125 (100.0%)	127 (100.0%)
Time from first known CSME diagnosis to randomization (yr)			
N	130	125	126
Mean (SD)	2.4 (3.2)	1.6 (2.0)	1.9 (2.4)
Median	1.2	1.1	1.1
Range	0.0-18.6	0.0-12.0	0.0-15.6
Treatments received for CSME			
N	130	125	127
Any treatment	92 (70.8%)	86 (68.8%)	88 (69.3%)
Focal / grid laser	84 (64.6%)	72 (57.6%)	79 (62.2%)
Steroids (intraocular or subtenon)	36 (27.7%)	32 (25.6%)	37 (29.1%)
Other	21 (16.2%)	27 (21.6%)	25 (19.7%)
Proliferative diabetic retinopathy (PDR)			
N	130	125	127
Active or previously treated PDR present	28 (21.5%)	31 (24.8%)	34 (26.8%)
Active neovascularization present	0 (0.0%)	0 (0.0%)	1 (0.8%)
Received panretinal photocoagulation (PRP) laser	21 (16.2%)	29 (23.2%)	29 (22.8%)
History of neovascular glaucoma (NVG)			
N	130	125	127
Yes	0 (0.0%)	0 (0.0%)	1 (0.8%)
No	130 (100.0%)	125 (100.0%)	126 (99.2%)

a Central foveal thickness (CFT) was defined as the center point thickness.

Reviewer's Comment:
All enrolled patients had clinically significant macular edema (CSME). The mean time since CSME diagnosis was 1.6-2.4 years prior to randomization.

Approximately 7-12% of randomized patients, all of whom had clinically significant macular edema (CSME), did not have NPDR. Note that the case report forms recorded diabetic history using the following questions:

- *Is non-proliferative diabetic retinopathy (NPDR) present in the study eye?*
- *Is active or previously treated proliferative diabetic retinopathy (PDR) present in the study eye?*
- *If yes, is there active neovascularization in the study eye?*

Thus, it was possible for patients to be counted in both the NPDR and PDR categories.

Table 6.1.1.2-7
Targeted Medical History and Baseline Characteristics

Diagnosis	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
OCULAR			
Glaucoma	15 (11.5%)	14 (11.2%)	21 (16.5%)
Dry AMD	2 (1.5%)	4 (3.2%)	0 (0.0%)
Wet AMD	0 (0.0%)	1 (0.8%)	1 (0.8%)
SYSTEMIC			
Diabetes mellitus	130 (100.0%)	125 (100.0%)	127 (100.0%)
Hypertension	103 (79.2%)	97 (77.6%)	101 (79.5%)
Cardiovascular	48 (36.9%)	30 (24.0%)	41 (32.3%)
Myocardial infarction	17 (13.1%)	12 (9.6%)	19 (15.0%)
Angina	16 (12.3%)	11 (8.8%)	11 (8.7%)
Coronary artery disease (CAD)	33 (25.4%)	20 (16.0%)	23 (18.1%)
Neurovascular	10 (7.7%)	6 (4.8%)	10 (7.9%)
Cerebrovascular accident (stroke)	6 (4.6%)	3 (2.4%)	7 (5.5%)
Transient ischemic attack	6 (4.6%)	2 (1.6%)	2 (1.6%)
Clotting / bleeding disorders	10 (7.7%)	7 (5.6%)	7 (5.5%)
Prior non-ocular hemorrhage	1 (0.8%)	1 (0.8%)	1 (0.8%)
Renal	10 (7.7%)	15 (12.0%)	22 (17.3%)

Reviewer's Comment:
Glaucoma, hypertension and cardiovascular disease were the most frequent concomitant diseases. A higher percentage of patients in the sham group had a history of coronary artery disease, angina and transient ischemic attacks when compared to the ranibizumab treatment groups.

A higher percentage of patients in the ranibizumab 0.5-mg group had a history of myocardial infarction, cerebrovascular accident (stroke) and renal diagnoses when compared to both the ranibizumab 0.3-mg treatment group.

The ranibizumab 0.3-mg group had fewer patients with hypertension, myocardial infarction, coronary artery disease and cerebrovascular accident compared to the other treatment groups.

Table 6.1.1.2-8
Prior Ocular Therapies and Procedures in the Study Eye

Type of Therapy	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Any prior ocular therapies	108 (83.1%)	103 (82.4%)	103 (81.1%)
Intravitreal anti-VEGF treatment	20 (15.4%)	21 (16.8%)	18 (14.2%)
Intravitreal steroids	32 (24.6%)	31 (24.8%)	35 (27.6%)
Medication – Other	5 (3.8%)	6 (4.8%)	4 (3.1%)
Laser, focal, or grid laser	83 (63.8%)	73 (58.4%)	76 (59.8%)
Pan retinal photocoagulation (PRP) laser	25 (19.2%)	34 (27.2%)	37 (29.1%)
Vitrectomy	1 (0.8%)	0 (0.0%)	0 (0.0%)
Other	38 (29.2%)	40 (32.0%)	45 (35.4%)

6.1.1.3 Subject Disposition

Table 6.1.1.3-1
Analysis Populations

Analysis Population	No. (%) of Subjects		
	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Randomized subjects (ITT)	130 (100%)	125 (100%)	127 (100%)
Per-protocol subjects	96 (73.8%)	91 (72.8%)	93 (73.2%)
Pharmacokinetic evaluable subjects	125 (96.2%)	121 (96.8%)	123 (96.9%)
Safety-evaluable subjects [a]	127 (97.7%)	125 (100.0%)	124 (97.6%)

a Treatment groups for the safety evaluable population were defined according to the actual treatment received rather than the treatment assigned.

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

Table 6.1.1.3-2
Subject Disposition and Primary Reason for Discontinuation

Status / Primary Reason for Discontinuation	Number (%) of Subjects		
	Sham/0.5 mg RBZ (n=130)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=127)
Received study drug	127 (97.7%)	125 (100%)	124 (97.6%)
Completed study through Month 24	108 (83.1%)	105 (84.0%)	110 (86.6%)
Completed study through Month 36	102 (78.5%)	98 (78.4%)	98 (77.2%)
Discontinued study prior to Month 36			
Total	28 (21.5%)	27 (21.6%)	17 (13.4%)
Death	3 (2.3%)	5 (4.0%)	10 (7.9%)
Adverse event	3 (2.3%)	1 (0.8%)	1 (0.8%)
Lost to follow-up	3 (2.3%)	3 (2.4%)	3 (2.4%)
Physician's decision	1 (0.8%)	2 (1.6%)	2 (1.6%)
Subject's decision	12 (9.2%)	11 (8.8%)	10 (7.9%)
Subject noncompliance	5 (3.8%)	2 (1.6%)	1 (0.8%)
Subject's condition mandated other therapeutic intervention	1 (0.8%)	3 (2.4%)	2 (1.6%)
Discontinued treatment prior to Month 36			
Total	30 (23.1%)	37 (29.6%)	29 (22.8%)
Death	3 (2.3%)	5 (4.0%)	9 (7.0%)
Adverse event	5 (3.8%)	3 (2.4%)	5 (3.9%)
Lost to follow-up	2 (1.5%)	3 (2.4%)	2 (1.6%)
Physician's decision	0 (0.0%)	2 (1.6%)	0 (0.0%)
Subject's decision	12 (9.2%)	16 (12.8%)	10 (7.9%)
Subject noncompliance	4 (3.1%)	1 (0.8%)	1 (0.8%)
Subject's condition mandated other therapeutic intervention	4 (3.1%)	5 (4.0%)	1 (0.8%)

a Some subjects remained in the study after treatment discontinuation. Only the primary reason for discontinuation was solicited so there could be differences in the number of subjects listing death as the reason for discontinuation (e.g., for a subject who died, the AE that led to death may have been the primary reason for discontinuation from treatment).

Reviewer's Comment:
Three hundred and twenty three subjects completed Month 24 (85%) and two hundred and ninety-eight subjects completed Month 36 (78%). Prior to Month 36, a total of seventy-two subjects discontinued the study, 28 (22%) from the sham group, 27 (22%) from the ranibizumab 0.3-mg group and 17 (13%) from the ranibizumab 0.5-mg group.

The major reason for treatment/study discontinuation was 'Subject's Decision'. 'Adverse event' was the reason for study/treatment discontinuation in less than 4% of subjects in each treatment group.

Table 6.1.1.3-3
Major Protocol Deviations during the 36-Month Study Period

Deviation	Sham/0.5 mg RBZ (N=130)	0.3 mg RBZ (N=125)	0.5 mg RBZ (N=127)
Any deviation	**12 (9.2%)**	**15 (12.0%)**	**8 (6.3%)**
Treatment error: received wrong treatment	5 (3.8%)	3 (2.4%)	3 (2.4%)
Received anti-VEGF treatment in study eye other than study drug	1 (0.8%)	1 (0.8%)	0
Received anti-VEGF treatment in the fellow eye other than per-protocol Genentech-supplied open label ranibizumab	6 (4.6%)	12 (9.6%)	5 (3.9%)
Received intravitreal or subtenon corticosteroid treatment in the study eye	2 (1.5%)	0	0

Note: Table entries are number (%) of subjects with the deviations of the type specified. Multiple incidents per subject were counted only once.

Reviewer's Comments:
The number of major protocol deviations was highest in the ranibizumab 0.3-mg treatment group. The most frequent major protocol deviation in each treatment group was receiving anti-VEGF treatment in the fellow eye other than per-protocol Genentech-supplied open-label ranibizumab.

Table 6.1.1.3-4
Concurrent Ocular Therapies and Procedures in the Study Eye during the 24-month Treatment Period

Ocular Procedure	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Any concurrent ocular procedure	29 (22.3%)	23 (18.4%)	21 (16.5%)
DME related (AC paracentesis, PPV, etc.)	5 (3.8%)	0 (0.0%)	1 (0.8%)
Cataract related (CE with lens implant, capsulotomy, etc.)	18 (13.8%)	17 (13.6%)	13 (10.2%)
Glaucoma related - laser procedures	1 (0.8%)	0 (0.0%)	2 (1.6%)
Vitreoretinal disease (non AMD) related – vitreoretinal surgery	1 (0.8%)	2 (1.6%)	1 (0.8%)
Diabetic retinopathy related - vitreoretinal surgery	5 (3.8%)	0 (0.0%)	1 (0.8%)
Other	2 (1.5%)	5 (4.0%)	4 (3.1%)

Table 6.1.1.3-5
Concurrent Ocular Therapies and Procedures in the Fellow Eye during the 24-month Treatment Period

Ocular Procedure	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Any concurrent ocular procedure	20 (15.4%)	25 (20.0%)	29 (22.8%)
DME related (AC paracentesis, PPV, etc.)	2 (1.5%)	3 (2.4%)	3 (2.4%)
Cataract related (CE with lens implant, capsulotomy, etc.)	14 (10.8%)	16 (12.8%)	16 (12.6%)
Glaucoma related - laser procedures	1 (0.8%)	1 (0.8%)	3 (2.4%)
Vitreoretinal disease (non AMD) related – vitreoretinal surgery	0 (0.0%)	2 (1.6%)	2 (1.6%)
Diabetic retinopathy related - vitreoretinal surgery	3 (2.3%)	3 (2.4%)	5 (3.9%)
Other	1 (0.8%)	1 (0.8%)	2 (1.6%)

Reviewer's Comment:
In both the study and fellow eyes, the most frequent concurrent ocular procedures were cataract related.

Table 6.1.1.3-6
Rescue Laser Treatment in the Study Eye during the 36-month Treatment Period

Ocular Procedure	Sham/RBZ 0.5 mg (N=130)	0.3 mg RBZ (N=125)	0.5 mg RBZ (N=127)
Received macular (focal or grid) rescue laser treatment	94 (72.3%)	46 (36.8%)	27 (21.3%)
Number of macular rescue laser treatments per subject			
Mean (SD)	1.7 (1.6)	0.9 (1.8)	0.4 (0.9)
Range	0 - 7	0 - 11	0 - 6
Time to first macular rescue laser treatment (days from Day 0)			
N	94	46	27
Mean (SD)	217.5 (192.5)	294.1 (223.4)	339.6 (249.8)
Median	127.5	219.0	210.0
Range	84-1052	82-973	86-819
Received Panretinal photocoagulation (PRP) laser treatment	18 (13.8%)	4 (3.2%)	3 (2.4%)
Number of PRP laser treatments per subject			
Mean (SD)	0.2 (0.7)	0.0 (0.01)	0.1 (0.5)
Range	0 - 4	0 - 1	0 - 6
0	112 (86.2%)	121 (96.8%)	124 (97.6%)

Ocular Procedure	Sham/RBZ 0.5 mg (N=130)	0.3 mg RBZ (N=125)	0.5 mg RBZ (N=127)
1	10 (7.7%)	4 (3.2%)	1 (0.8%)
2	5 (3.8%)	0	1 (0.8%)
3	2 (1.5%)	0	0
4	1 (0.8%)	0	0
6	0	0	1 (0.8%)

Reviewer's Comment:
Seventy-two percent of sham patients received macular rescue laser treatment compared to 37% and 21% in the 0.3-mg and 0.5-mg ranibizumab treatment groups respectively.

Approximately 97% of ranibizumab patients did not receive PRP compared to 86% of sham patients received no PRP. Macular rescue laser treatments occurred much more frequently than PRP laser treatments.

Table 6.1.1.3-7
Discontinued Subjects and Reason for Discontinuation during the 24-Month Controlled Treatment Period Study FVF4168g

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
		Sham Group	
S14667	51502	Physician's decision – Vitreous hemorrhage in study eye	NT
S14726	50904	Non-compliance	183
	50914	Lost to follow-up	264
S15399	50801	Subject's condition mandated other therapeutic intervention (Steroid use – Basedow's disease)	514
S15420	51405	AE – Bilateral breast cancer AE – Worsening DME in fellow eye AE – Worsening of DME in study eye	377
S15901	52401	AE – Myocardial infarction, renal failure	128
S15995	50306	Subject's condition mandated other therapeutic intervention. Worsening of diabetic retinal edema in the fellow eye – Treated with bevacizumab, triamcinolone	239
S16084	54701	Subject's decision	248
S16120	54605	Subject's decision	66
S16248	51802	Subject's decision	211
S16248	51808	Lost to follow-up	400
S16352	52902	AE – Gastric ulcer, CHF, syncope, MI, GI bleed (Subject's decision)	514
S16473	54502	Subject's decision	147
S16491	51703	Subject's decision	92
	51705	AE – Subhyaloid hemorrhage in study eye	95
S16612	55901	Subject's condition mandated other therapeutic intervention. – Treated with bevacizumab	218
S16669	52702	Lost to follow-up	NT
S16786	52201	Non-compliance	327

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
S16892	54201	AE – Worsening COPD, GI bleed	75
S17651	53203	Non-compliance	NT
S17653	56602	AE – Worsening DME in study eye and fellow eye; Retinal aneurysm	180
S17958	52101	AE – Vitreous hemorrhage in study eye	120
	52107	Subject's condition mandated other therapeutic intervention – Avastin injection, fellow eye AE – Tractional retinal detachment in fellow eye	239
S20917	57402	Death – Stroke, myocardial infarction	146
S22387	57209	Subject's decision	92
S23058	57605	Subject's decision	89
		0.3 mg Group	
S14726	50903	Subject's decision	495
	50905	Subject's condition mandated other therapeutic intervention – Avastin injection, fellow eye for worsening DME	548
	50920	Subject's decision	148
	50923	Death – Cardiac arrest	425
S14764	54001	Subject's decision	79
S14768	52603	Lost to follow-up	96
S15514	51103	Subject's decision	80
S15901	52403	Lost to follow-up	95
S15995	50310	Subject's decision	301
S16120	54602	AE- Hypoglycemia, CVA	58
	54604	Physician's decision to withdraw	54
S16151	51003	Subject's decision	397
S16276	54104	Non-compliance	238
S16352	52906	Subject's condition mandated other therapeutic intervention – Avastin injection in fellow eye	231
	52914	Worsening of diabetic retinal edema in the fellow eye – Treated with bevacizumab	93
S16410	50703	Death – Respiratory failure, exacerbated cardiac failure, acute myocardial infarction	503
	50718	Death - Aortic aneurysm rupture	548
S16491	51702	Subject's condition mandated other therapeutic intervention – Avastin injection in fellow eye	594
S16787	55604	Subject's decision	695
S16892	54202	AE – Acute MI, pneumonia, diabetic nephropathy	409
S17958	52102	Subject's condition mandated other therapeutic intervention – Avastin injection in fellow eye	547
S20854	57302	AE – Worsening cataract Death – Stroke	519 722
	57308	Subject's decision	111
S21029	57504	Subject's decision	37
S22387	57206	AE – Endophthalmitis	225
S23648	58105	Subject's decision	58
		0.5 mg Group	
S14688	53401	AE – Cerebrovascular accident	NT
S14726	50917	Death – Worsening CAD, Cardiac arrest	286
S14743	56503	Subject's decision	268
S15901	52402	Death – Congestive heart failure, CAD, stroke	120

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
S15995	50309	Subject's condition mandated other therapeutic intervention – Avastin injection in fellow eye	93
S16069	50101	Subject's decision	505
S16248	51810	Subject's decision	303
S16276	54103	Subject's condition mandated other therapeutic intervention; Did not meet inclusion criteria	NT
S16350	53502	Physician's decision	NT
	53504	AE – Renal failure Death - Cardiac arrest	520
S16473	54503	AE – Polymyalgica rheumatica exacerbation	35
S16691	53304	Death – Pneumonia	64
S16786	52203	Death – Acute renal failure, Squamous cell CA of tongue	490
	52204	Death – Suicide (CO poisoning)	322
S16959	53803	Subject's decision	34
S17653	56601	AE – Retinal neovascularization, vitreomacular traction	208
S17958	52103	Non-compliance	266
	52104	Lost to follow-up	549
S21029	57519	AE – Endophthalmitis	394

NT = Not treated

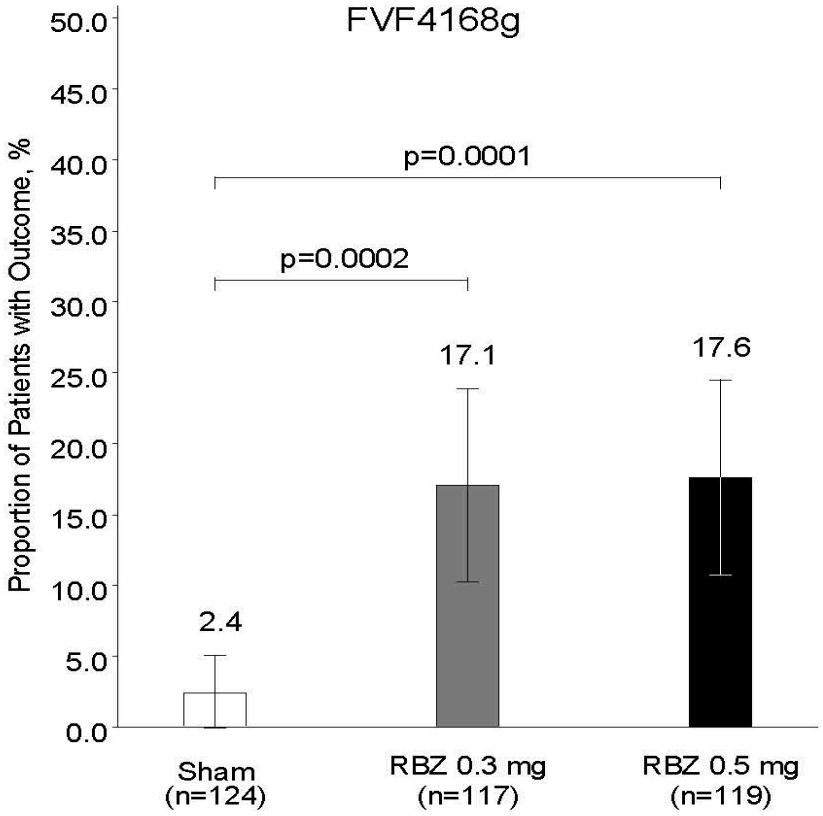
6.1.1.4 Analysis of Diabetic Retinopathy - Main Efficacy Measure

Table 6.1.1.4-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
n (%)	3 (2.4%)	20 (17.1%)	21 (17.6%)
95% CI for percentage [a]	(0.0%, 5.1%)	(10.3%, 23.9%)	(10.8%, 24.5%)
Difference in % (vs. sham) [b]		14.5%	15.0%
95% CI of the difference [b]		(7.4%, 21.7%)	(7.8%, 22.2%)
p-value (vs. sham) [c]		0.0002	0.0001

Source: Module 5.3.5.3 ISE Table 12
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Figure 6.1.1.4-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 6
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Reviewer's Comment:
There were 17.1% and 17.6% of subjects in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, who experienced a ≥ 3-step improvement from baseline in ETDRS DR Severity Score at Month 24. When compared to sham, the differences were statistically significant for both treatment groups.

Except for the proportion of subjects with a 3-step or greater worsening from baseline in the ETDRS diabetic retinopathy severity level as assessed by the central reading center using fundus photography which was pre-specified in the original study protocol all

analyses are exploratory in nature. Family-wise type I error is not strongly controlled among the DR-related analyses.

6.1.1.5 Analysis of Supportive Diabetic Retinopathy Outcome Measure(s)

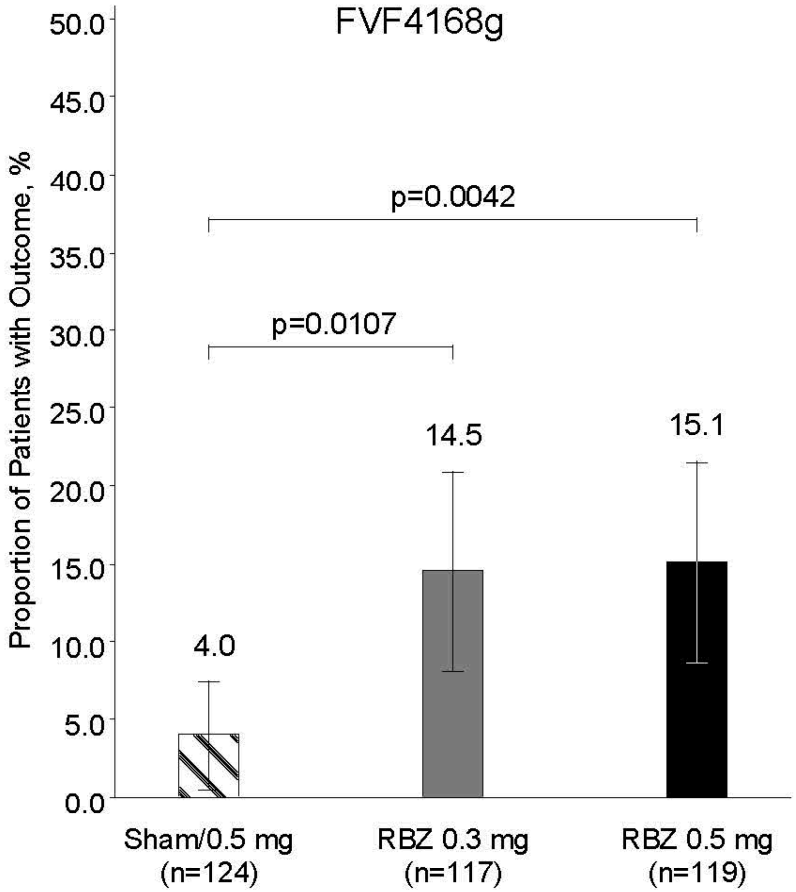
Proportion of subjects with a ≥ 3-step improvement from baseline in the ETDRS DR severity score at 36 months, as assessed by the central reading center using FP.

Table 6.1.1.5-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham / 0.5 mg RBZ n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
n (%)	5 (4.0%)	17 (14.5%)	18 (15.1%)
95% CI for percentage [a]	(0.6%, 7.5%)	(8.1%, 20.9%)	(8.7%, 21.6%)
Difference in % (vs. sham) [b]		9.7%	10.8%
95% CI of the difference [b]		(2.7%, 16.7%)	(3.8%, 17.8%)
p-value (vs. sham) [c]		0.0107	0.0042

Source: Module 5.3.5.3 ISE Figure 6
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

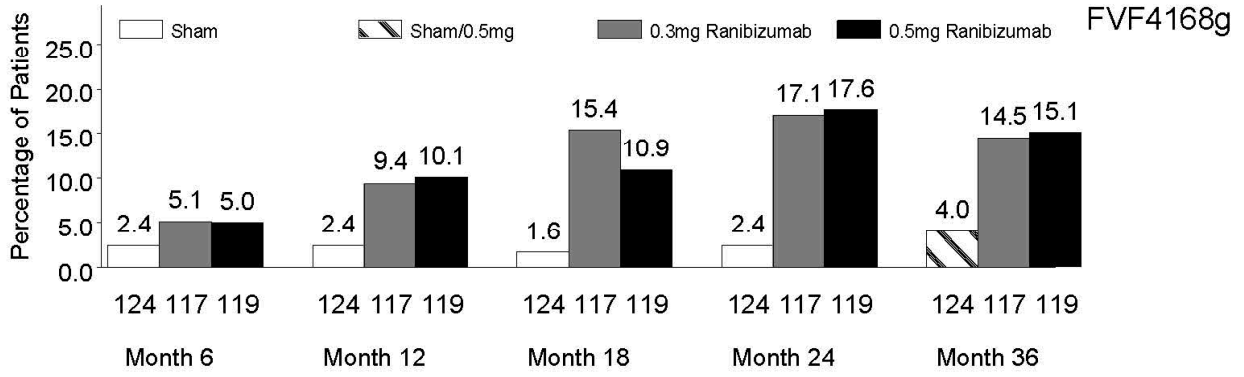
Figure 6.1.1.5-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 7
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Reviewer's Comment:
The proportion of subjects in the 0.3-mg and 0.5-mg ranibizumab groups who had a ≥ 3-step improvement from baseline in ETDRS DR Severity Score at Month 36 was 14.5% and 15.1%, respectively. When compared with the sham / 0.5-mg group, the differences were statistically significant with p-values, 0.0107 and 0.0042, for the 0.3-mg and 0.5-mg ranibizumab groups, respectively. Thus, the treatment group difference was maintained through Month 36.

Figure 6.1.1.5-2
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 9

Reviewer's Comment:
The proportion of subjects with a ≥ 3-step improvement from baseline in ETDRS DR Severity Score in the study eye was greater in the ranibizumab treatment groups beginning at Month 6, statistically significant at Month 12 and maintained through Month 36.

The percentage of subjects with a ≥ 3-step improvement from baseline in ETDRS DR Severity Score in the Sham/0.5 mg crossover group increased slightly by Month 36.

Proportion of subjects with a ≥ 2-step improvement from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP

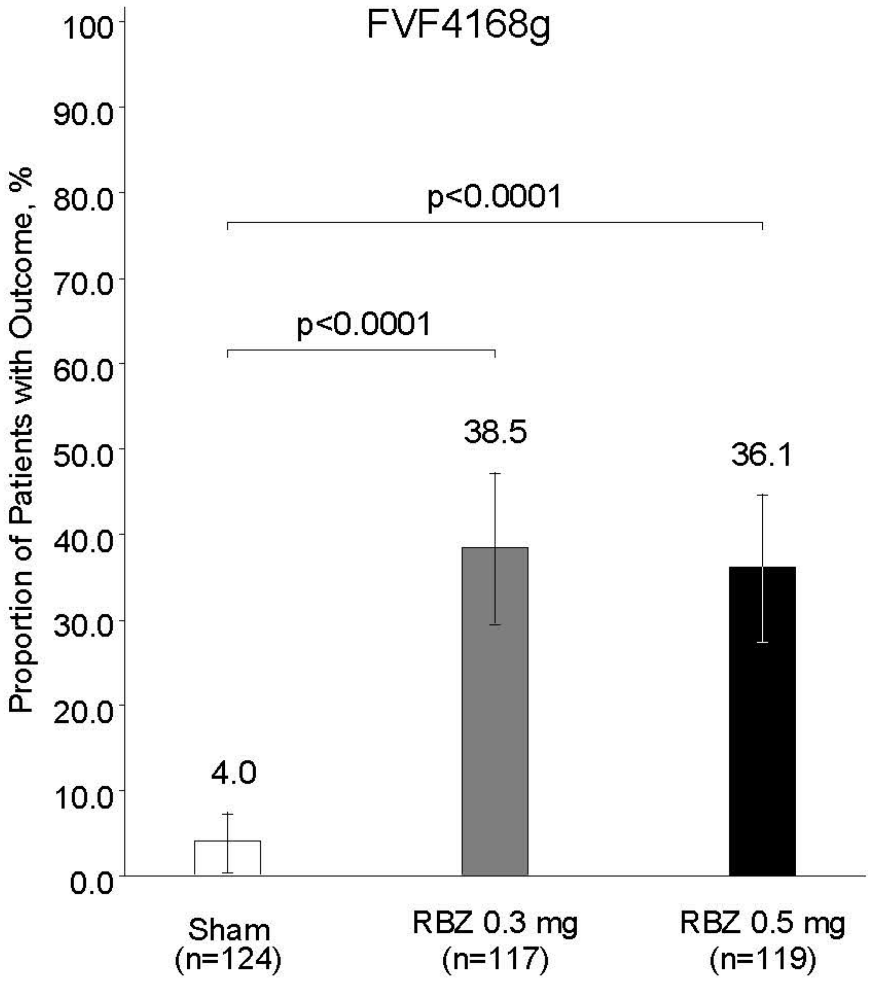
Table 6.1.1.5-2
Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
Month 24			
n (%)	5 (4.0%)	45 (38.5%)	43 (36.1%)
95% CI for percentage [a]	(0.6%, 7.5%)	(29.6%, 47.3%)	(27.5%, 44.8%)
Difference in % (vs. sham) [b]		34.8%	32.0%
95% CI of the difference [b]		(25.5%, 44.1%)	(22.8%, 41.2%)
p-value (vs. sham) [c]		<0.0001	<0.0001
	Sham/ 0.5 mg RBZ n=124	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=119**
Month 36			
n (%)	29 (23.4%)	46 (39.3%)	45 (37.8%)
95% CI for percentage [a]	(15.9%, 30.8%)	(30.5%, 48.2%)	(29.1%, 46.5%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		16.9%	14.3%
95% CI of the difference [b]		(5.5%, 28.3%)	(3.0%, 25.6%)
p-value (vs. sham) [c]		0.0058	0.0172

Source: Module 5.3.5.3 ISE Table 14
Note: P-values are for testing difference between Ran bizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

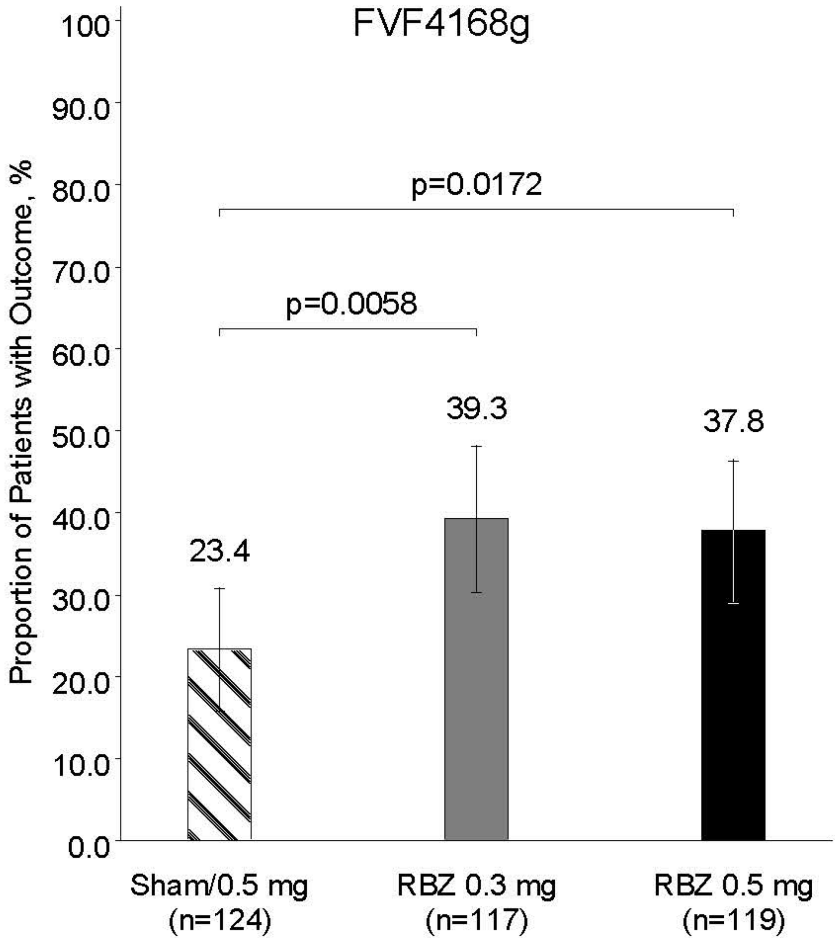
Reviewer's Comment:
At Month 24, a ≥ 2-step improvement in ETDRS DR Severity Score in the study eye was seen in 39% and 36% of patients in the ranibizumab 0.3-mg and 0.5-mg treatment groups respectively compared to 4% in the sham treatment group. The treatment group differences were statistically significant at p<0.0001 for both groups. The treatment group difference compared to sham/0.5-mg RBZ was maintained at Month 36, p=0.0058 and p=0.0172 levels for the ranibizumab 0.3-mg and 0.5-mg groups.

Figure 6.1.1.5-3
Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



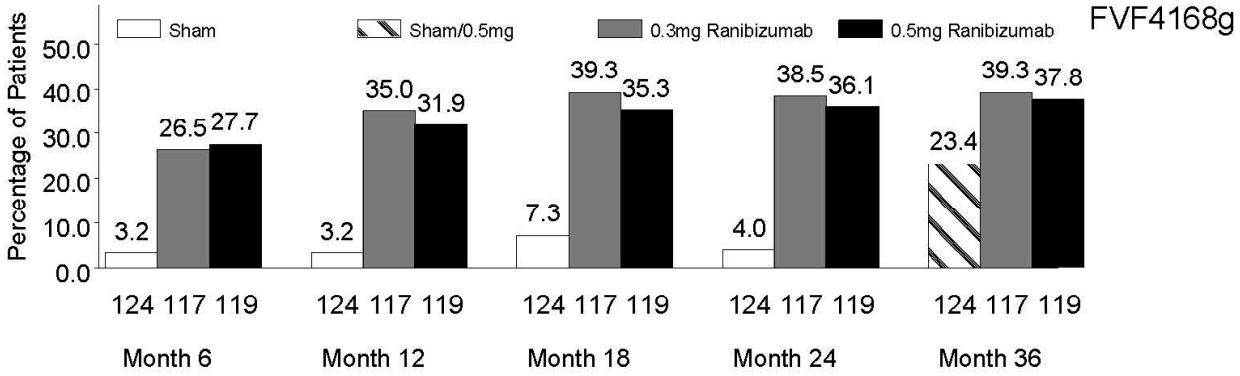
Source: Module 5.3.5.3 ISE Figure 10
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.1.5-4
Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 11
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.1.5-5
Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 12

Reviewer's Comment:
The proportion of subjects with a ≥ 2 -step improvement from baseline in ETDRS DR Severity Score in the study eye was greater in the ranibizumab treatment groups beginning at Month 6, statistically significant at Month 12 and maintained through Month 36.

The proportion of subjects who achieved the lower threshold of ≥ 2-step improvement from baseline in ETDRS DR severity score in the study eye was greater in all treatment groups from Month 6 – Month 36. There was a relatively greater increase in the proportion of sham/0.5 mg group subjects seen from Month 24 to Month 36.

Proportion of subjects with a ≥ 3-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP

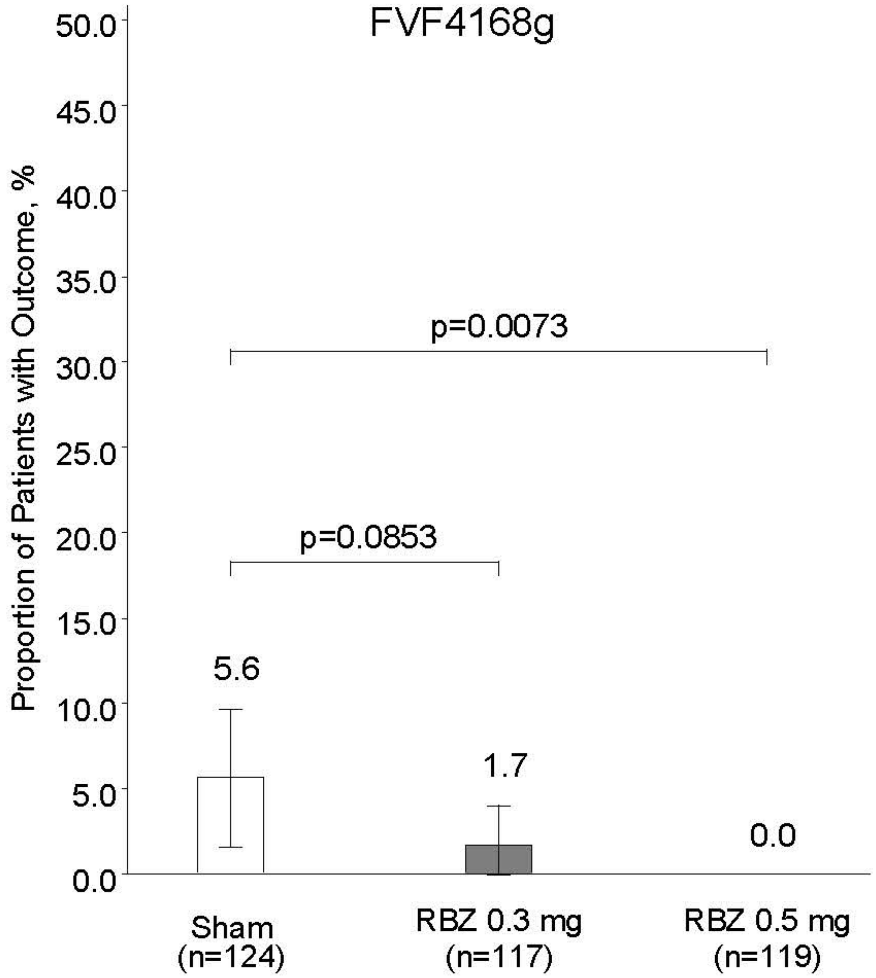
Table 6.1.1.5-3
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
Month 24			
n (%)	7 (5.6%)	2 (1.7%)	0
95% CI for percentage [a]	(1.6%, 9.7%)	(0.0%, 4.1%)	(0.0%, 0.0%)
Difference in % (vs. sham) [b]		-4.3%	-5.8%
95% CI of the difference [b]		(-9.3%, 0.8%)	(-9.8%, -1.7%)
p-value (vs. sham) [c]		0.0853	0.0073
	Sham/ 0.5 mg RBZ n=124	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=119**
Month 36			
n (%)	4 (3.2%)	1 (0.9%)	1 (0.8%)
95% CI for percentage [a]	(0.1%, 6.3%)	(0.0%, 2.5%)	(0.0%, 2.5%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		-2.3%	-2.4%
95% CI of the difference [b]		(-6.0%, 1.3%)	(-5.8%, 1.0%)
p-value (vs. sham) [c]		0.2222	0.1920

Source: Module 5.3.5.3 ISE Table 15
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

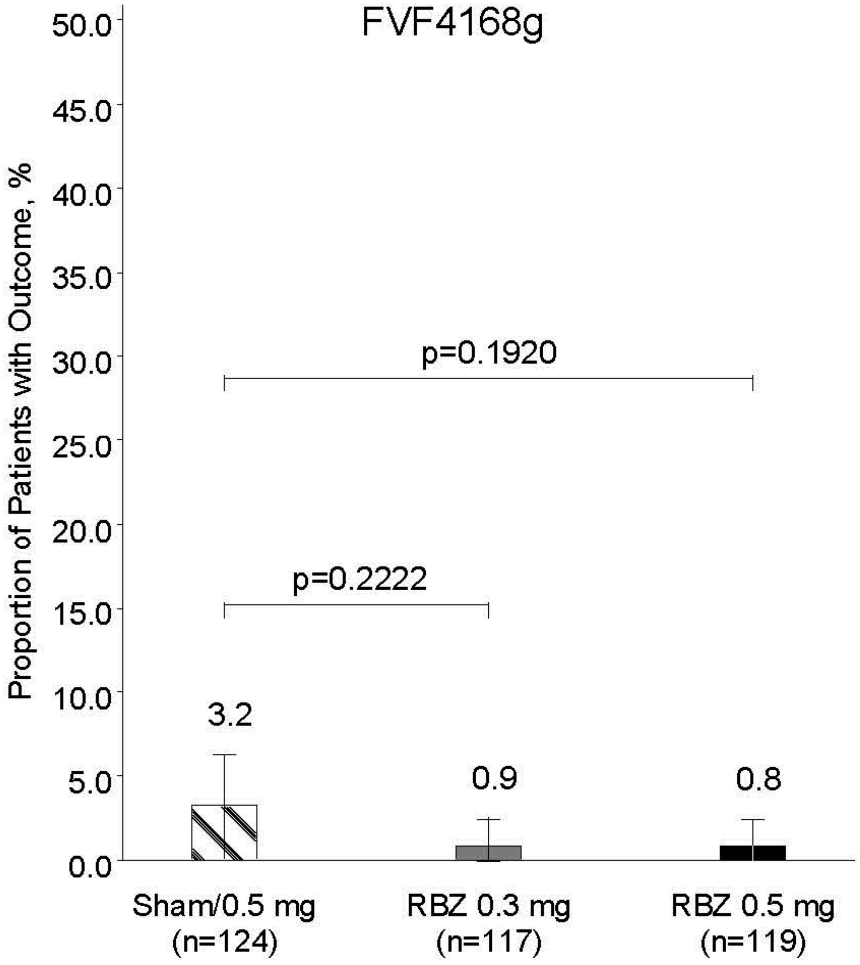
Reviewer's Comment:
Though numerically fewer subjects experienced a three-step or greater worsening from baseline in ETDRS Diabetic Retinopathy Severity score in the ranibizumab groups compared to sham at 24 months and 36 months, the differences were only statistically significant for the ranibizumab 0.5 mg group at Month 24. It was not statistically significant for the 0.3-mg ranibizumab group compared to sham at Month 24 or sham/0.5-mg at Month 36.

Figure 6.1.1.5-6
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



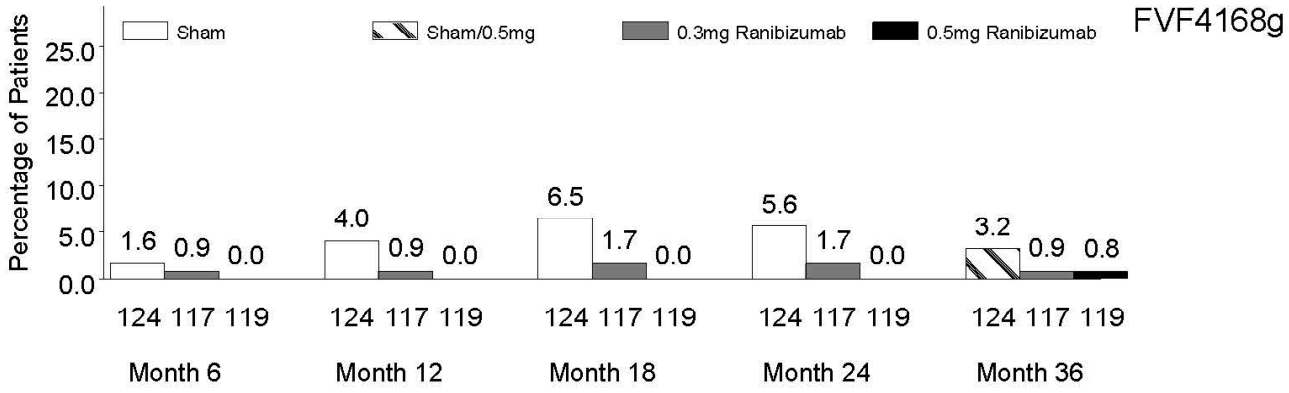
Source: Module 5.3.5.3 ISE Figure 14
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.1.5-7
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 15
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.1.5-8
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 17

Reviewer's Comment:
The proportion of subjects with worsening diabetic retinopathy through Month 24 was greatest in the sham group, less in the 0.3-mg ranibizumab group and none in the 0.5-mg ranibizumab group showing a dose dependent halt in progression of DR.

Proportion of subjects with a ≥ 2-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP

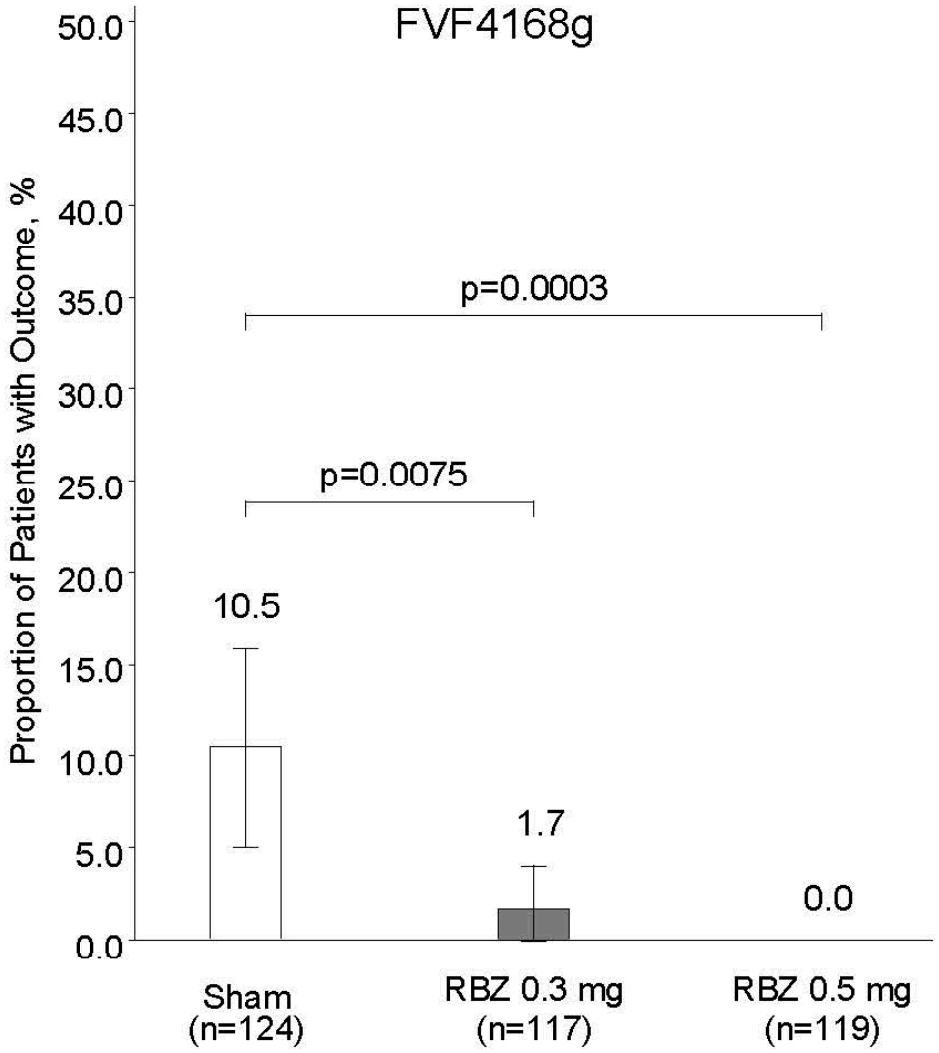
Table 6.1.1.5-4
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham n=124	0.3 mg RBZ n=117	0.5 mg RBZ n=119
Month 24			
n (%)	13 (10.5%)	2 (1.7%)	0
95% CI for percentage [a]	(5.1%, 15.9%)	(0.0%, 4.1%)	(0.0%, 0.0%)
Difference in % (vs. sham) [b]		-8.5%	-10.6%
95% CI of the difference [b]		(-14.4%, -2.6%)	(-16.0%, -5.3%)
p-value (vs. sham) [c]		0.0075	0.0003
	Sham/ 0.5 mg RBZ n=124	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=119**
Month 36			
n (%)	11 (8.9%)	1 (0.9%)	2 (1.7%)
95% CI for percentage [a]	(3.9%, 13.9%)	(0.0%, 2.5%)	(0.0%, 4.0%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		-7.8%	-7.2%
95% CI of the difference [b]		(-13.1%, -2.5%)	(-12.7%, -1.7%)
p-value (vs. sham) [c]		0.0065	0.0140

Source: Module 5.3.5.3 ISE Table 16
Note: P-values are for testing difference between ran bizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

Reviewer's Comment:
Fewer subjects experienced a two-step or greater worsening from baseline in ETDRS Diabetic Retinopathy Severity Level in the ranibizumab groups compared to sham and sham/0.5-mg RBZ groups at 24 and 36 months in a dose dependent manner. The differences were statistically significant for each ranibizumab comparison to sham or sham/0.5 mg.

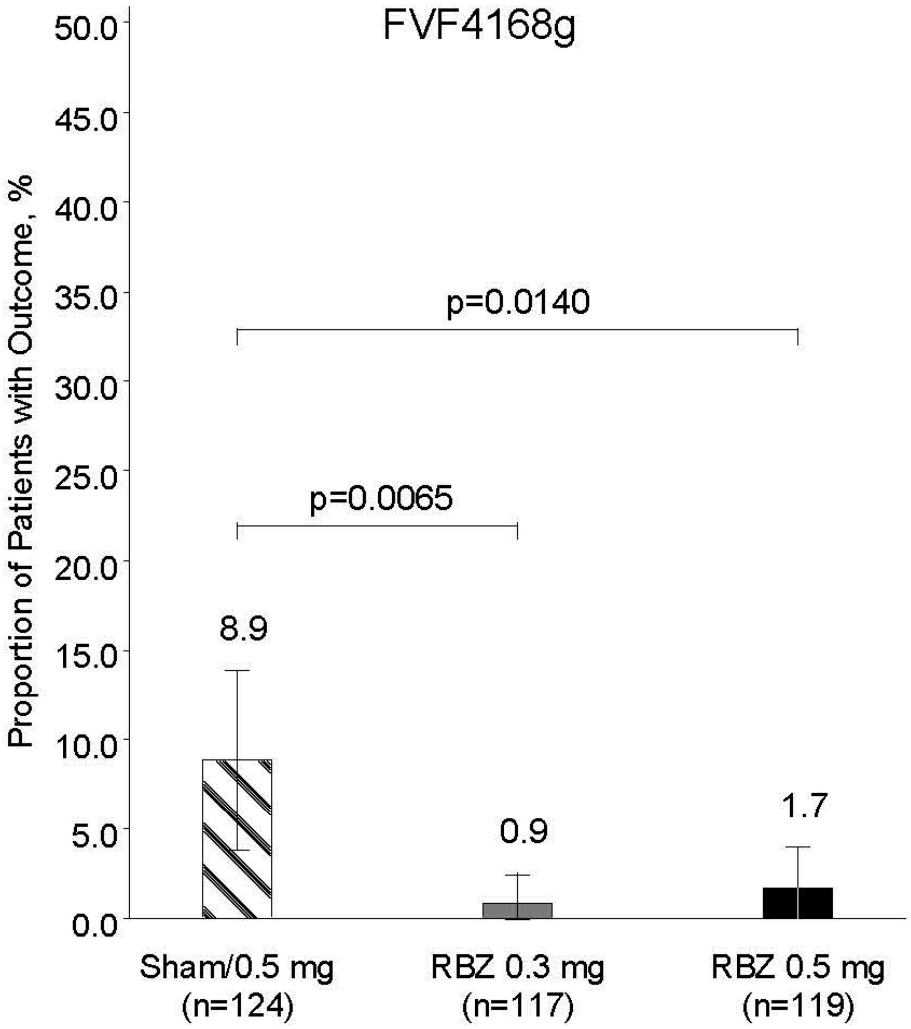
Figure 6.1.1.5-9
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 18
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

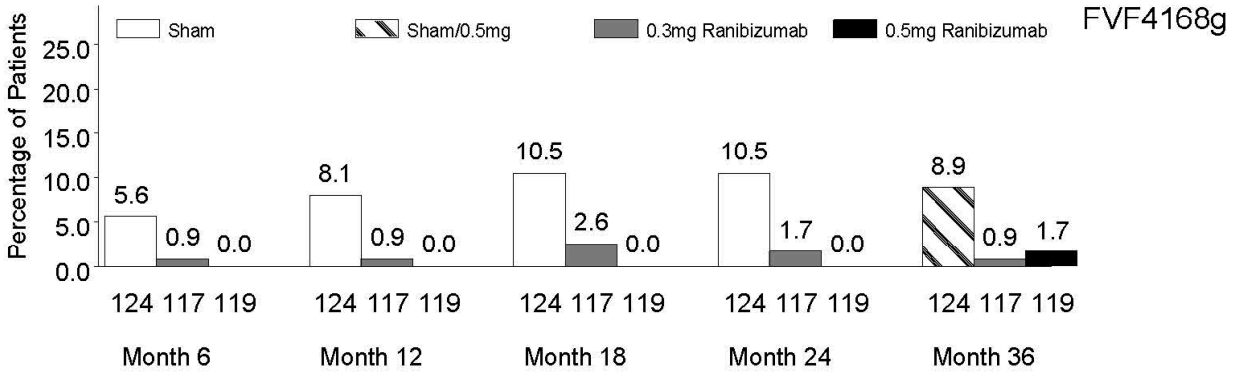
Reviewer's Comment:
The proportion of subjects with worsening diabetic retinopathy through Month 24 was greatest in the sham group, less in the 0.3-mg ranibizumab group and none in the 0.5-mg ranibizumab group showing a dose dependent halt in progression of DR.

Figure 6.1.1.5-10
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 19
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.1.5-11
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 21

Reviewer's Comment:
The proportion of subjects with worsening diabetic retinopathy through Month 24 was greatest in the sham / sham/0.5-mg RBZ group, less in the 0.3-mg ranibizumab group and none in the 0.5-mg ranibizumab group until Month 36, showing a dose dependent halt in progression of DR.

Proportion of subjects progressing to PDR as determined by the indirect ophthalmoscopy assessment of the presence of neovascularization on the optic disc, elsewhere on the retina, or iris by Month 24 and 36.

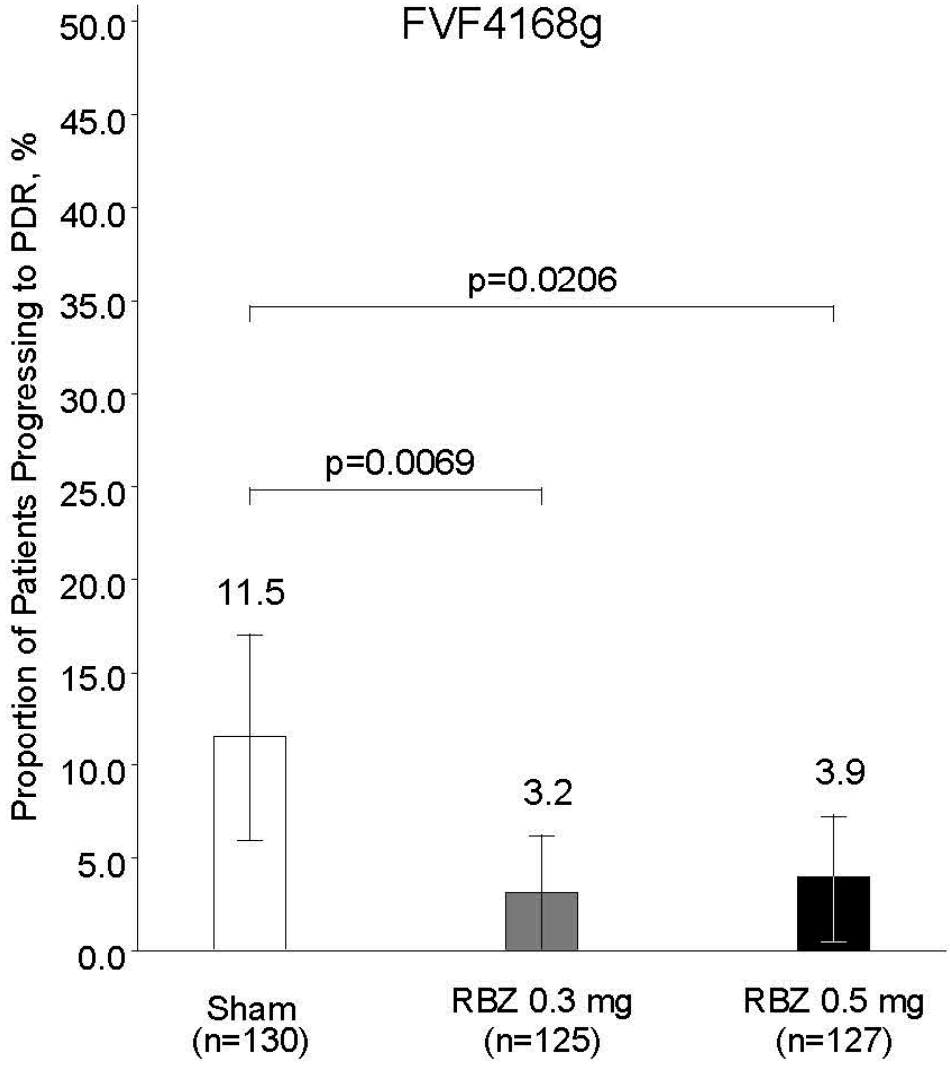
Table 6.1.1.5-5
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye at Month 24 and Month 36 (Study FVF4168g)

	Sham n=130	0.3 mg RBZ n=125	0.5 mg RBZ n=127
Month 24			
n (%)	15 (11.5%)	4 (3.2%)	5 (3.9%)
95% CI for percentage [a]	(6.0%, 17.0%)	(0.1%, 6.3%)	(0.6%, 7.3%)
Difference in % (vs. sham) [b]		-9.1%	-7.8%
95% CI of the difference [b]		(-15.4%, -2.7%)	(-14.1%, -1.4%)
p-value (vs. sham) [c]		0.0069	0.0206
	Sham/ 0.5 mg RBZ n=130	**0.3 mg RBZ n=125**	**0.5 mg RBZ n=127**
Month 36			
n (%)	18 (13.8%)	6 (4.8%)	7 (5.5%)
95% CI for percentage [a]	(7.9%, 19.8%)	(1.1%, 8.5%)	(1.5%, 9.5%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		-9.6%	-8.3%
95% CI of the difference [b]		(-16.9%, -2.2%)	(-15.3%, -1.3%)
p-value (vs. sham) [c]		0.0106	0.0251

Source: Module 5.3.5.3 ISE Table 17
Note: P-values are for testing difference between ran bizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

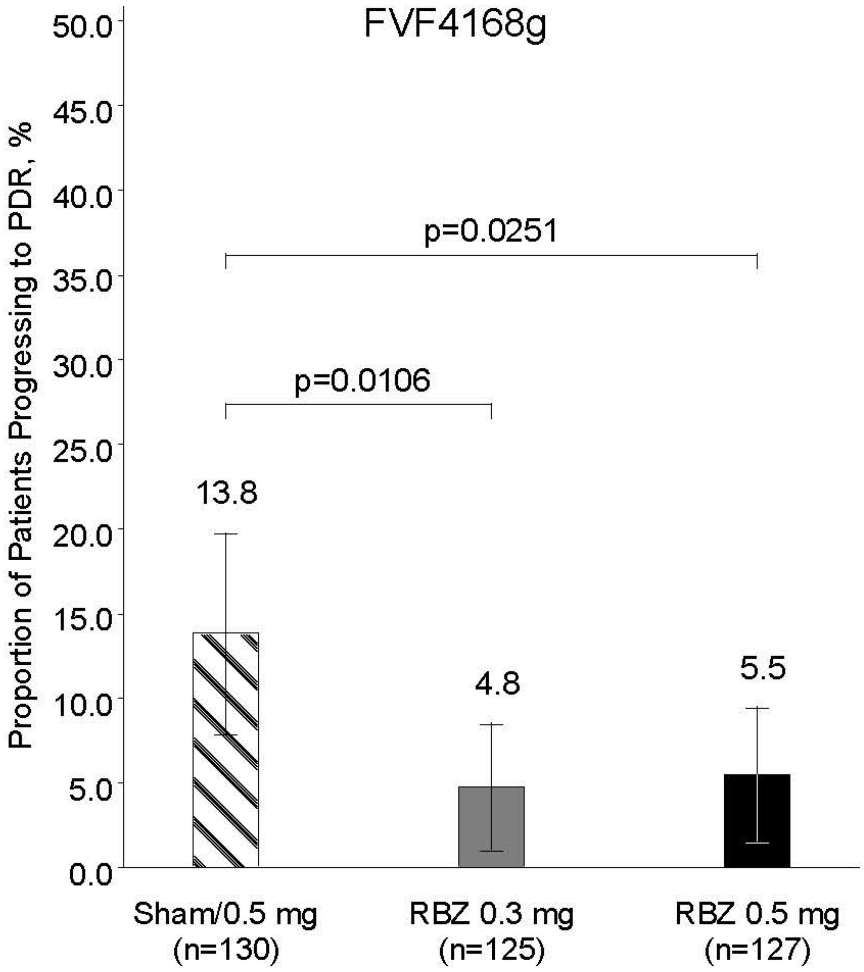
Reviewer's Comment:
The proportion of subjects who progressed to PDR in the ranibizumab groups compared to sham and sham/0.5-mg RBZ treatment groups at Month 24 and Month 36 was smaller and statistically significantly so for each of the four comparisons.

Figure 6.1.1.5-12
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye at Month 24



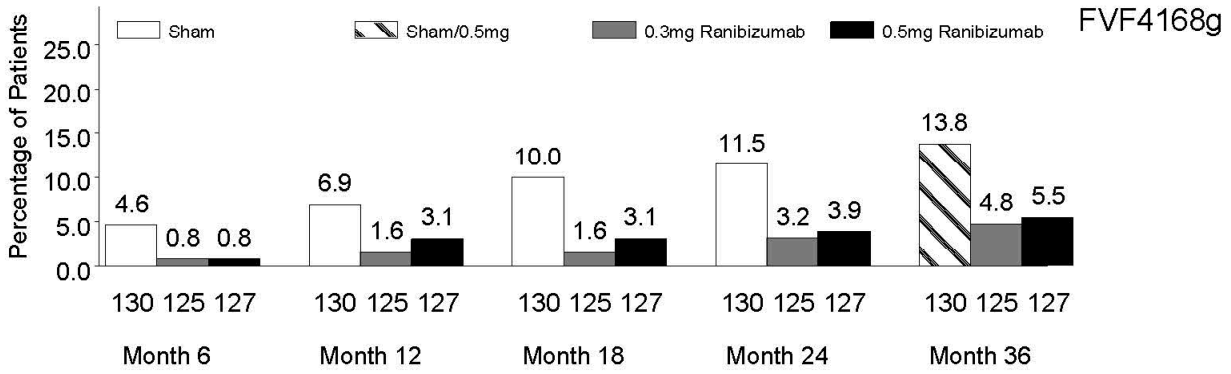
Source: Module 5.3.5.3 ISE Figure 22
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.1.5-13
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye at Month 36



Source: Module 5.3.5.3 ISE Figure 23
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.1.4-2
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye Over Time



Source: Module 5.3.5.3 ISE Figure 25

Reviewer's Comment:

The proportion of subjects who progressed to PDR in the ranibizumab groups compared to sham and sham/0.5-mg RBZ treatment groups at Month 24 and Month 36 was statistically significantly, although it is influenced by the baseline level of retinopathy. From Month 18 through Month 36, the proportion of subjects who progressed to PDR increased in each treatment group.

6.1.1.6 Other Endpoints

None.

6.1.1.7 Subpopulations

Demographic data, diagnoses, and baseline lesion characteristics between treatment groups within each study were comparable.

The number of patients within any particular 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.

Diabetic retinopathy is a disease seen only in adults; therefore, no pediatric trials were conducted for this drug product.

6.1.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant performed adequate dose ranging studies during the drug development program. Lucentis (ranibizumab) 0.3-mg and 0.5-mg dose have been demonstrated to be safe and effective in two Phase 3 clinical trials for the proposed indication. Studies have not been powered to determine a difference between the doses. The frequency of dosing needed is not well established.

6.1.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Reviewer's Comment:
No evidence of tolerance or withdrawal effects has been detected in any trials submitted in the original BLA 125156 for Lucentis (ranibizumab injection) or subsequent supplements.

6.1.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy or analysis issues.

6.1.2 Study FVF4170g (RISE)

6.1.2.1 Methods

The 24-month controlled data and 36-month final data from the Phase 3 study, FVF4170g, was reviewed in Supplement 076 which was approved on August 10, 2012. The 60-month data from the open label extension study was reviewed in S-105.

Study FVF4170g data is referenced in this supplemental BLA (S-106) to determine its safety and effectiveness [redacted] (b) (4)

6.1.2.2 Demographics

Table 6.1.2.2-1 Baseline Demographics and Characteristics Study FVF4170g

Demographic	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Age (yr)			
N	127	125	125
Mean (SD)	61.8 (9.8)	61.7 (8.9)	62.8 (10.0)
Range	39.0-85.0	38.0-82.0	21.0-87.0
Age group (yr)			
N	127	125	125
18 - <25	0	0	1 (0.8%)
25 - <35	0	0	0
35 - <45	5 (3.9%)	3 (2.4%)	4 (3.2%)
45 - <55	23 (18.1%)	24 (19.2%)	19 (15.2%)
55 - <65	51 (40.2%)	51 (40.8%)	38 (30.4%)
65 - <75	35 (27.6%)	36 (28.8%)	53 (42.4%)
75 - <85	12 (9.4%)	11 (8.8%)	9 (7.2%)
85 - <95	1 (0.8%)	0	1 (0.8%)
≥ 95	0	0	0
Sex, n (%)			
N	127	125	125
Male	74 (58.3%)	73 (58.4%)	65 (52.0%)
Female	53 (41.7%)	52 (41.6%)	60 (48.0%)
Ethnicity, n (%)			
N	127	125	125

Demographic	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Hispanic or Latino	24 (18.9%)	20 (16.0%)	25 (20.0%)
Not Hispanic or Latino	100 (78.7%)	102 (81.6%)	98 (78.4%)
Not available	3 (2.4%)	3 (2.4%)	2 (1.6%)
Race, n (%)			
N	127	125	125
Asian	6 (4.7%)	7 (5.6%)	7 (5.6%)
Black or African American	19 (15.0%)	18 (14.4%)	14 (11.2%)
Native Hawaiian/Other Pacific Islander	1 (0.8%)	2 (1.6%)	1 (0.8%)
White	101 (79.5%)	97 (77.6%)	97 (77.6%)
Not available	0	1 (0.8%)	6 (4.8%)
Duration of diabetes at randomization (yr)			
N	123	118	118
Mean (SD)	14.5 (9.9)	15.9 (9.9)	16.3 (8.5)
Range	0.2-57.1	0.5-55.1	0.5-41.0
Glycosylated hemoglobin (HbA_{1c})			
N	123	120	120
Mean (SD)	7.7 (1.5)	7.7 (1.5)	7.7 (1.4)
Glycosylated hemoglobin (HbA_{1c}) group			
N	123	120	120
≤ 8	80 (65.0%)	81 (67.5%)	82 (68.3%)
> 8	43 (35.0%)	39 (32.5%)	38 (31.7%)
Diastolic blood pressure (mmHg)			
N	126	125	125
Mean (SD)	77.3 (10.9)	77.0 (10.1)	76.4 (8.7
Range	52.0-110.0	50.0-110.0	60.0-97.0

Reviewer's Comment:
Two-thirds of the patients enrolled were age 55-75 years with the mean age being 62 years.

In approximately one-third of the subjects enrolled, diabetes was not under optimal glycemic control as measured by glycosylated hemoglobin (HgbA1c). The study excluded subjects with HgbA1c values greater than 12%. The American Diabetic Association recommends a value of ≤ 7% for non-pregnant adults.

Table 6.1.2.2-2
Baseline Ocular Characteristics in the Study Eye Study FVF4170g

Characteristic	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Visual acuity			
Number of letters (0-100)			
N	127	125	125
Mean (SD)	57.2 (11.1)	54.7 (12.6)	56.9 (11.6)
Range	29-72	23-85	23-77
Distribution, n (%)			
≤ 55	51 (40.2%)	59 (47.2%)	48 (38.4%)
> 55	76 (59.8%)	66 (52.8%)	77 (61.6%)
Approximate Snellen equivalent			
N	127	125	125
20/200 or worse	10 (7.9%)	17 (13.6%)	10 (8.0%)
Better than 20/200 to worse than 20/40	92 (72.4%)	91 (72.8%)	91 (72.8%)
20/40 or better	25 (19.7%)	17 (13.6%)	24 (19.2%)
Contrast sensitivity			
N	125	124	123
Mean (SD)	25.7 (5.5)	25.8 (6.3)	26.3 (5.5)
Range	12-36	7-37	8-36

Reviewer's Comment:
The treatment groups were similar with regard to baseline visual function characteristics.

Table 6.1.2.2-3
Baseline Fluorescein Angiography Characteristics in the Study Eye Study FVF4170g

Characteristic	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Total area of capillary loss in center, inner, and outer subfields, calculated (DA)			
n	111	107	118
Mean (SD)	0.137 (0.392)	0.162 (0.473)	0.172 (0.528)
Range	0.00-2.58	0.00-2.64	0.00-3.92
Total area of fluorescein leakage in center, inner and outer subfields, calculated (DA)			
n	123	121	122
Mean (SD)	9.166 (4.513)	8.700 (4.621)	8.196 (4.698)
Range	0.00-16.00	1.09-16.00	0.00-16.00
Total area of cystoid changes in center, inner, and outer subfields, calculated (DA)			
n	123	121	122
Mean (SD)	0.948 (1.371)	1.306 (1.768)	1.150 (1.949)
Range	0.00-6.10	0.00-9.10	0.00-12.97

Reviewer's Comment:
The treatment groups were similar with regard to the baseline fluorescein angiography characteristics in the study eye.

Table 6.1.2.2-4
Baseline Fundus Photography Characteristics of the Study Eye Study FVF4170g

Characteristic	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Total area of retinal thickening in central, inner, and outer subfields (DA)			
N	122	113	114
Mean (SD)	8.227 (3.897)	8.367 (4.223)	7.961 (4.212)
Range	1.01-16.00	0.00-16.00	0.92-16.00
ETDRS diabetic retinopathy severity level			
N	126	121	121
1 – DR severity level 10, 12 (DR absent)	0	1 (0.8%)	0
2 – DR severity level 14A-14C, 14Z, 15, 20 (DR questionable, microaneurysms only)	0	2 (1.7%)	2 (1.7%)
3 – DR severity level 35A-35F (mild NPDR)	17 (13.5%)	19 (15.7%)	25 (20.7%)
4 – DR severity level 43A, 43B (moderate NPDR)	21 (16.7%)	16 (13.2%)	16 (13.2%)
5 – DR severity level 47A-47D (moderately severe NPDR)	34 (27.0%)	39 (32.2%)	36 (29.8%)
6 – DR severity level 53A-53E (severe NPDR)	8 (6.3%)	5 (4.1%)	4 (3.3%)
7 – DR severity level 60,61A, 61B (mild PDR)	32 (25.4%)	32 (26.4%)	31 (25.6%)
8 – DR severity level 65A-65C (moderate PDR)	3 (2.4%)	2 (1.7%)	1 (0.8%)
9 – DR severity level 71A- 71D (high risk PDR)	0	1 (0.8%)	0
90 – DR severity level 90 (cannot grade)	11 (8.7%)	4 (3.3%)	6 (5.0%)

Reviewer's Comment:
Sixty to 65% of subjects had moderately severe NPDR or worse (DR severity level ≥ 47).

In each treatment group, the highest percentage of subjects had moderately severe NPDR (47), sham (27.0%), ranibizumab 0.3-mg (32.2%) and ranibizumab 0.5-mg (29.8%).

Five patients (4.2%) had no DR, questionable DR (DR severity level ≤ 20). One subject in the 0.3-mg ranibizumab group had high risk PDR (DR severity level - 71). The treatment groups were similarly balanced regarding the baseline study eye ETDRS diabetic retinopathy severity levels as assessed by fundus photography.

Table 6.1.2.2-5
Baseline Optical Coherence Tomography Characteristics of the Study Eye Study FVF4170g

Characteristic	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Central foveal thickness (µm)			
n	127	125	125
Mean (SD)	467.3 (152.0)	474.5 (174.8)	463.8 (144.0)
Median	456.0	445.0	447.0
Range	183-1046	144-1048	198-999
Distribution, n (%)			
< 450	61 (48.0%)	66 (52.8%)	66 (52.8%)
≥ 450	66 (52.0%)	59 (47.2%)	59 (47.2%)
Central subfield thickness (µm)			
n	109	115	111
Mean (SD)	463.9 (127.3)	463.7 (138.9)	455.6 (121.8)
Median	456.0	426.0	440.0
Range	224-803	269-1012	234-979
Distribution, n (%)			
< 450	54 (49.5%)	66 (57.4%)	59 (53.2%)
≥ 450	55 (50.5%)	49 (42.6%)	52 (46.8%)
Total retinal volume (mm^3)			
n	106	109	108
Mean (SD)	9.5 (2.0)	9.5 (2.2)	9.6 (2.2)
Median	9.1	9.3	9.4
Range	7-15	6-18	6-17

a Central foveal thickness (CFT) was defined as the center point thickness.

Reviewer's Comment:
The treatment groups were similar regarding the baseline fundus characteristics as assessed by optical coherence tomography.

Table 6.1.2.2-6
Diabetic Macular Edema History of the Study Eye Study FVF4170g

	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Non-proliferative diabetic retinopathy (NPDR)			
NPDR present			
N	127	125	125
Yes	112 (88.2%)	111 (88.8%)	114 (91.2%)
No	15 (11.8%)	14 (11.2%)	11 (8.8%)
Time from first known NPDR diagnosis to randomization (yr)			
N	112	109	113
Mean (SD)	2.3 (2.5)	2.2 (2.3)	2.5 (3.1)
Median	1.6	1.5	1.5
Range	0.0-12.3	0.1-10.5	0.0-21.0
Clinically significant macular edema (CSME)			
N	127	125	125
Yes	127 (100.0%)	125 (100.0%)	125 (100.0%)
Time from first known CSME diagnosis to randomization (yr)			
N	127	124	123
Mean (SD)	2.3 (3.0)	2.1 (2.2)	2.1 (2.1)
Median	1.2	1.4	1.4
Range	0.0-15.7	0.1-10.5	0.0-8.5
Treatments received for CSME			
N	127	125	125
Any treatment	94 (74.0%)	94 (75.2%)	102 (81.6%)
Focal / grid laser	86 (67.7%)	86 (68.8%)	90 (72.0%)
Steroids (intraocular or subtenon)	35 (27.6%)	39 (31.2%)	50 (40.0%)
Other	21 (16.5%)	20 (16.0%)	21 (16.8%)
Proliferative diabetic retinopathy (PDR)			
N	127	125	125
Active or previously treated PDR present	34 (26.8%)	28 (22.4%)	32 (25.6%)
Active neovascularization present	0 (0.0%)	0 (0.0%)	0 (0.0%)
Received panretinal photocoagulation (PRP) laser	31 (24.4%)	24 (19.2%)	27 (21.6%)
History of neovascular glaucoma (NVG)			
N	127	125	125
Yes	0 (0.0%)	0 (0.0%)	1 (0.8%)
No	127 (100.0%)	125 (100.0%)	124 (99.2%)

a Central foveal thickness (CFT) was defined as the center point thickness.

Reviewer's Comment:
All enrolled subjects had clinically significant macular edema (CSME). The mean time since CSME diagnosis was 2.1-2.3 years prior to randomization. Approximately 8-12% of patients did not have NPDR.

Note that the case report forms recorded diabetic history using the following questions:

- *Is nonproliferative diabetic retinopathy (NPDR) present in the study eye?*
- *Is active or previously treated proliferative diabetic retinopathy (PDR) present in the study eye?*
- *If yes, is there active neovascularization in the study eye?*

Thus, it was possible for patients to be counted in both the NPDR and PDR categories.

Table 6.1.2.2-7
Targeted Medical History and Baseline Characteristics
Study FVF4170g: Randomized Subjects

Diagnosis	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
OCULAR			
Glaucoma	12 (9.4%)	18 (14.4%)	21 (16.8%)
Dry AMD	5 (3.9%)	6 (4.8%)	6 (4.8%)
Wet AMD	1 (0.8%)	2 (1.6%)	4 (3.2%)
SYSTEMIC			
Diabetes mellitus	127 (100.0%)	125 (100.0%)	125 (100.0%)
Hypertension	110 (86.6%)	109 (87.2%)	101 (80.8%)
Cardiovascular	41 (32.3%)	46 (36.8%)	46 (36.8%)
Myocardial infarction	17 (13.4%)	21 (16.8%)	14 (11.2%)
Angina	10 (7.9%)	14 (11.2%)	10 (8.0%)
Coronary artery disease	31 (24.4%)	33 (26.4%)	31 (25.0%)
Neurovascular	16 (12.6%)	17 (13.6%)	13 (10.4%)
Cerebrovascular accident (stroke)	12 (9.4%)	12 (9.6%)	10 (8.0%)
Transient ischemic attack	6 (4.7%)	9 (7.2%)	6 (4.8%)
Clotting / bleeding disorders	11 (8.7%)	12 (9.6%)	10 (8.0%)
Prior non-ocular hemorrhage	3 (2.4%)	2 (1.6%)	1 (0.8%)
Renal	23 (18.1%)	24 (19.2%)	19 (15.3%)[a]

a One subject had a missing renal assessment record (n=124).

Reviewer's Comment:
Glaucoma, hypertension and cardiovascular disease were the most frequent concomitant diseases. When compared to the other treatment groups, a higher percentage of patients

in the ranibizumab 0.3-mg group had a history of myocardial infarction, angina, transient ischemic attacks and renal diagnoses.

Table 6.1.2.2-8
Prior Ocular Therapies and Procedures in the Study Eye FVF4170g

Type of Therapy	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Any prior ocular therapies	104 (81.9%)	101 (80.8%)	112 (89.6%)
Intravitreal anti-VEGF treatment	15 (11.8%)	19 (15.2%)	21 (16.8%)
Intravitreal steroids	32 (25.2%)	37 (29.6%)	46 (36.8%)
Medication – Other	5 (3.9%)	3 (2.4%)	6 (4.8%)
Laser, focal, or grid laser	87 (68.5%)	88 (70.4%)	90 (72.0%)
Pan retinal photocoagulation (PRP) laser	32 (25.2%)	27 (21.6%)	27 (21.6%)
Vitrectomy	1 (0.8%)	0 (0.0%)	1 (0.8%)
Other	37 (29.1%)	38 (30.4%)	50 (40.0%)

6.1.2.3 Subject Disposition

Table 6.1.2.3-1
Study FVF4170g : Analysis Populations

	Sham / 0.5 mg RBZ (n=127)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=125)
Randomized subjects (ITT)	127 (100%)	125 (100%)	125 (100%)
Per-protocol subjects	83 (65.4%)	93 (74.4%)	84 (67.2%)
Safety-evaluable subjects [a]	123 (96.9%)	125 (100%)	126 (100.8%)
Pharmacokinetic-evaluable subjects	125 (98.4%)	121 (96.8%)	122 (97.6%)

a Treatment groups for the safety evaluable population were defined according to the actual treatment received rather than the treatment assigned.

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

Table 6.1.2.3-2
Subject Disposition and Primary Reason for Discontinuation during the 36-Month Treatment Period (Study FVF4170g)

Status / Primary Reason for Discontinuation	Number (%) of Subjects		
	Sham / 0.5 mg RBZ (n=127)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=125)
Received study drug	126 (99.2%)	124 (99.2%)	124 (99.2%)
Completed study through Month 24	102 (80.3%)	105 (84.0%)	106 (84.8%)
Completed study through Month 36	86 (67.7%)	98 (78.4%)	100 (80.0%)
Discontinued study prior to Month 36			
Total	41 (32.3%)	27 (21.6%)	25 (20.0%)
Death	4 (3.1%)	6 (4.8%)	4 (3.2%)
Adverse event	1 (0.8%)	4 (3.2%)	4 (3.2%)
Lost to follow-up	10 (7.9%)	5 (4.0%)	5 (4.0%)
Physician's decision	3 (2.4%)	2 (1.6%)	1 (0.8%)
Subject's decision	19 (15.0%)	9 (7.2%)	8 (6.4%)
Subject noncompliance	1 (0.8%)	1 (0.8%)	2 (1.6%)
Subject's condition mandated other therapeutic intervention	3 (2.4%)	0	1 (0.8%)
Discontinued treatment prior to Month 36			
Total	42 (33.1%)	28 (22.4%)	30 (24.0%)
Death	3 (2.4%)	6 (4.8%)	4 (3.2%)
Adverse event	4 (3.1%)	5 (4.0%)	5 (4.0%)
Lost to follow-up	10 (7.9%)	5 (4.0%)	3 (2.4%)
Physician's decision	2 (1.6%)	1 (0.8%)	2 (1.6%)
Subject's decision	17 (13.4%)	10 (8.0%)	12 (9.6%)
Subject noncompliance	1 (0.8%)	1 (0.8%)	2 (1.6%)
Subject's condition mandated other therapeutic intervention	5 (3.9%)	0 (0.0%)	2 (1.6%)

a Some subjects remained in the study after treatment discontinuation. Only the primary reason for discontinuation was solicited so there could be differences in the number or subjects listing death as the reason for discontinuation (e.g., for a subject who died, the AE that led to death may have been the primary reason for discontinuation from treatment).

Reviewer's Comment:
Three hundred and thirteen subjects completed Month 24 (83%) and 284 (75%) completed Month 36, a total of 93 subjects discontinued the study - 41 (32%) from the sham group, 27 (22%) from the ranibizumab 0.3-mg group and 25 (20%) from the ranibizumab 0.5-mg group.

The major reason for treatment/study discontinuation was 'Subject's Decision'. 'Adverse event' was the reason for study/treatment discontinuation in ≤ 4% of subjects in each treatment group.

Table 6.1.2.3-3
Major Protocol Deviations during the 36-Month Study Period

Deviation	Sham (N=130)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=127)
Any deviation	**13 (10.2%)**	**7 (5.6%)**	**11 (8.8%)**
Treatment error: received wrong treatment	2 (1.6%)	4 (3.2%)	0 (0.0%)
Received anti-VEGF treatment in study eye other than study drug before discontinuing the study drug	2 (1.6%)	0	1 (0.8%)
Received anti-VEGF treatment in the fellow eye other than per-protocol Genentech-supplied open label ranibizumab	9 (7.1%)	3 (2.4%)	8 (6.4%)
Received intravitreal or subtenon corticosteroid treatment in the study eye before discontinuing study drug	1 (0.8%)	0 (0.0%)	1 (0.8%)

Note: Table entries are number (%) of subjects with the deviations of the type specified. Multiple incidents per subject were counted only once.

Reviewer's Comments:
The number of major protocol deviations was highest in the sham treatment group.

The most frequent major protocol deviation in each treatment group was receiving anti-VEGF treatment in the fellow eye other than per-protocol Genentech-supplied open-label ranibizumab.

Table 6.1.2.3-4
Concurrent Ocular Therapies and Procedures in the Study Eye during the 24-Month Controlled Treatment Period

Ocular Procedure	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Any concurrent ocular procedure	20 (15.7%)	17 (13.6%)	25 (20.0%)
DME related (AC paracentesis, PPV, etc.)	4 (3.1%)	0 (0.0%)	2 (1.6%)
Cataract related (CE with lens implant, capsulotomy, etc.)	11 (8.7%)	12 (9.6%)	13 (10.4%)
Glaucoma related - laser procedures	1 (0.8%)	1 (0.8%)	2 (1.6%)
Vitreoretinal disease (non AMD) related – vitreoretinal surgery	2 (1.6%)	0 (0.0%)	1 (0.8%)
Diabetic retinopathy related - vitreoretinal surgery	2 (1.6%)	0 (0.0%)	2 (1.6%)
Other	1 (0.8%)	4 (3.2%)	8 (6.4%)

Table 6.1.2.3-5
Concurrent Ocular Therapies and Procedures in the Fellow Eye during the 24-Month Controlled Treatment Period

Ocular Procedure	Sham (N=127)	Ranibizumab 0.3 mg (N=125)	Ranibizumab 0.5 mg (N=125)
Any concurrent ocular procedure	23 (18.1%)	19 (15.2%)	23 (18.4%)
DME related (AC paracentesis, PPV, etc.)	2 (1.6%)	2 (1.6%)	6 (4.8%)
Cataract related (CE with lens implant, capsulotomy, etc.)	17 (13.4%)	13 (10.4%)	13 (10.4%)
Glaucoma related - laser procedures	1 (0.8%)	1 (0.8%)	2 (1.6%)
Vitreoretinal disease (non AMD) related – vitreoretinal surgery	0 (0.0%)	4 (3.2%)	1 (0.8%)
Diabetic retinopathy related - vitreoretinal surgery	2 (1.6%)	4 (3.2%)	2 (1.6%)
Other	3 (2.4%)	1 (0.8%)	6 (4.8%)

Reviewer's Comments:
In both the study and fellow eyes, the number of concurrent ocular procedures was lowest in the ranibizumab 0.3-mg treatment group. The most frequent concurrent ocular procedures were cataract related and were similar in all treatment groups.

Table 6.1.2.3-6
Macular Rescue Laser Treatment and Panretinal Photocoagulation Laser Treatment in the Study Eye during the 36-Month Treatment Period

Ocular Procedure	Sham/0.5 mg RBZ (N=127)	0.3 mg RBZ (N=125)	0.5 mg RBZ (N=125)
Received macular (focal or grid) rescue laser treatment	94 (74.0%)	51 (40.8%)	47 (37.6%)
Number of macular rescue laser treatments per subject			
Mean (SD)	1.9 (1.8)	0.8 (1.4)	0.9 (1.5)
Range	0-7	0-9	0-8
Time to first macular rescue laser treatment (days from Day 0)			
N	94	51	47
Mean (SD)	157.1 (98.1)	217.1 (208.8)	232.8 (231.3)
Median	115.5	126.0	121.0
Range	63-549	8-929	84-948
Received Panretinal photocoagulation (PRP) laser treatment			
Number of PRP laser treatments per subject	1323	1407	1378
Mean (SD)	0.2 (0.7)	0.0 (0.0)	0.0 (0.2)
Range	0 – 4	0 – 0	0 - 2

0	111 (87.4%)	125 (100.0%)	122 (97.6%)
1	9 (7.1%)	0	2 (1.6%)
2	4 (3.1%)	0	1 (0.8%)
3	2 (1.6%)	0	0
4	1 (0.8%)	0	0

Reviewer's Comments:

Seventy four percent of the subjects in the sham treatment group received macular rescue laser treatment almost twice as many as in either ranibizumab treatment group.

98 - 100% of ranibizumab treated subjects did not require panretinal photocoagulation compared to 87% of sham/0.5-mg RBZ subjects.

Table 6.1.2.3-7
Subjects Who Discontinued Treatment and Reason for Discontinuation during the 24-Month Controlled Treatment Period Study FVF4170g

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
		Sham Group	
S15923	70201	Subject's decision	666
S15941	70314	Death - Unknown cause	629
S16013	74001	AE – Diabetic retinopathy worsening - retinal edema, vitreous hemorrhage	358
S16036	71601	AE – Cerebrovascular accident	485
S16104	71901	Subject's decision	451
S16108	73307	Subject's decision	188
S16121	70101	Subject's decision	522
S16162	75603	Subject's condition mandated other therapeutic intervention – Avastin injection	96
S16175	72204	Subject's decision	90
	73403	AE – Transient ischemic attack, myocardial infarction	631
S16177	73415	Subject's condition mandated other therapeutic intervention – Avastin injection	115
S16196	71801	Patient was randomized in error	NT
	72403	Lost to follow-up	305
	72405	Lost to follow-up	210
	72406	Subject's decision	92
S16199	72412	Subject's decision	119
S16200	71501	Subject's decision	396
S16202	73508	Lost to follow-up	540
	73509	Subject's decision	302
	72608	Subject's decision	393
S16475	72610	Subject's decision	243
S16515	73205	Subject's decision	213
S16640	75001	Subject's condition mandated other therapeutic intervention – Avastin injection	445
S16647	74501	AE – Ischemic stroke	167

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
	73007	Death – Cardiac arrest, renal failure	568
S16716	73010	Lost to follow-up	1
S17151	76101	Physician's decision	64
	74703	Subject's decision	64
S18051	74709	Physician's decision	60
	72903	Subject's condition mandated other therapeutic intervention – Avastin injection	181
	72911	Subject non-compliance	121
S18056	72919	Lost to follow-up	483
S18997	77001	Subject's condition mandated other therapeutic intervention – Avastin injection	446
		0.3 mg Group	
S15999	70904	Subject's decision	148
S16013	74002	AE – Cerebrovascular accident, cardiac infection	121
S16109	71205	Subject's decision	210
S16147	71402	AE – Septic shock, pelvic abscess	154
S16157	75202	Physician's decision	NT
S16175	72206	Subject non-compliance	104
S16178	73101	Subject's decision	608
S16199	72416	AE – Renal failure AE – Advanced dilated cardiomyopathy, Death - Cardiac arrest	141 235 270
S16202	73502	Subject's decision	155
	73506	Subject's decision	468
S16370	70704	Subject's decision	126
S16475	72603	Death – Respiratory failure, end stage renal disease, myocardial infarction	416
S 16515	73203	AE – Malignant hepatic neoplasm	100
S16716	73002	Physician's decision	183
S16725	75803	Subject's decision	464
S16838	75301	AE – Skin ulcer	227
S18056	72909	Lost to follow-up	695
	72914	Lost to follow-up	577
S18247	75704	Death – Clostridium difficile infection	514
S18344	76503	Lost to follow-up	604
S18379	76001	Lost to follow-up	356
		0.5 mg Group	
S15954	73902	Physician's decision	703
S16016	71303	AE – Diabetic retinal edema, study and fellow eyes	246
S16108	73305	AE – Metastatic breast cancer	65
S16156	73605	Subject's decision	151
S16160	70501	AE – Aortic stenosis, congestive heart failure, acute cholecystitis, pleural effusion	548
S16172	70801	Subject's decision	449
S16175	72211	Subject's condition mandated other therapeutic	92

Study Site ID	Subject ID	Reason for Discontinuation	Study Day
		intervention – Avastin injection	
S16177	73401	Subject's decision	449
	73405	Subject's decision	99
S16199	72402	Lost to follow-up	302
	72411	Subject's decision	60
S16202	73501	Non-compliance	540
S16411	76403	Physician's decision	383
S16475	72611	AE – Cerebrovascular accident	438
S16515	73201	AE – Eye pain	NT
S16522	75403	Subject's condition mandated other therapeutic intervention – Avastin injection	485
S16647	74502	Subject's decision	394
S16670	76205	AE – GI hemorrhage x 3 Death – Severe CVA	546 688
S16671	75102	Subject's decision	514
S16716	73001	Death – Worsening CAD, Cardiac arrest	597
	73004	Subject's decision	251
	73006	Lost to follow-up	120
S16725	75802	Lost to follow-up	648
S16838	75309	Subject's decision	335
S18056	71912	Death – Perforation of the large intestine	141
S18247	75703	Death –Ventricular fibrillation	421
S20883	77401	Subject's decision	14

Reviewer's Comment:
The major reason for treatment discontinuation was 'Subject decision'.

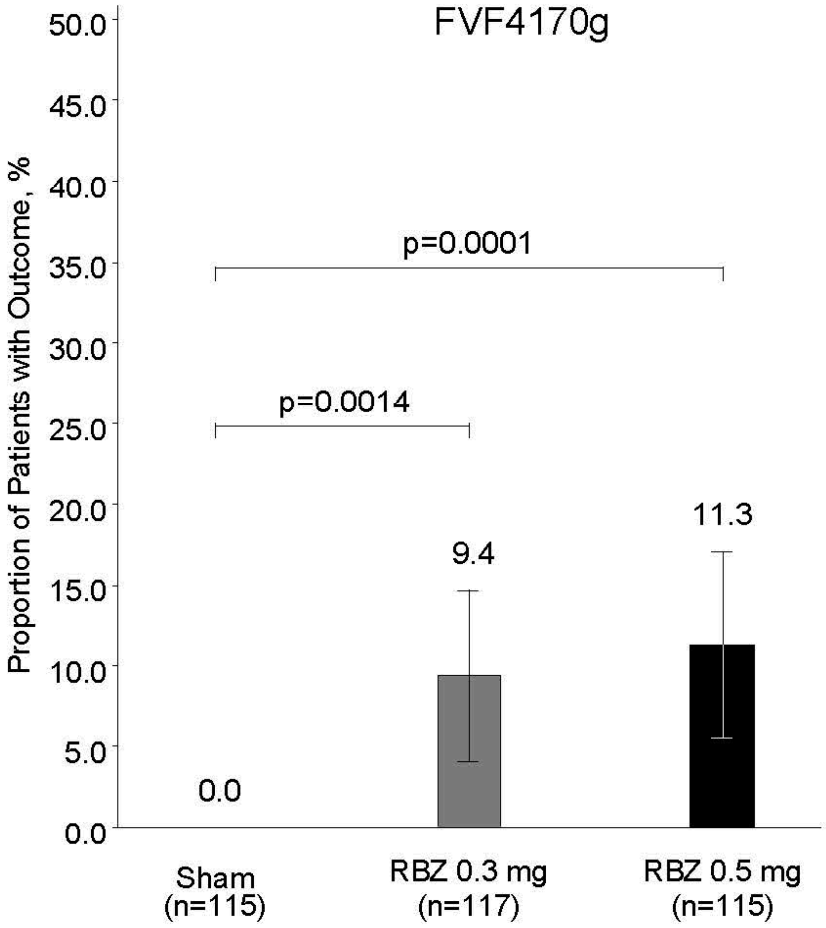
6.1.2.4 Analysis of Diabetic Retinopathy – Main Efficacy Measure

Table 6.1.2.4-1 Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24 (Subjects with a Valid Score at Baseline; LOCF)

	Sham n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=115
n (%)	0	11 (9.4%)	13 (11.3%)
95% CI for percentage [a]	(0.0%, 0.0%)	(4.1%, 14.7%)	(5.5%, 17.1%)
Difference in % (vs. sham) [b]		8.9%	11.7%
95% CI of the difference [b]		(4.0%, 13.7%)	(5.9%, 17.4%)
p-value (vs. sham) [c]		0.0014	0.0001

Source: Module 5.3.5.3 ISE Table 12
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Figure 6.1.2.4-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 6
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

Reviewer's Comment:

There were 9% and 11% of subjects in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, who experienced a ≥ 3-step improvement from baseline in ETDRS DR Severity score at Month 24. When compared to sham the differences were statistically significant for both treatment groups.

6.1.2.5 Analysis of Supportive Diabetic Retinopathy Outcome Measure(s)

Reviewer's Comment:
Except for the proportion of subjects with a 3-step or greater worsening from baseline in the ETDRS diabetic retinopathy severity level as assessed by the central reading center using fundus photography which was pre-specified in the original study protocol all analyses are exploratory in nature. Family-wise type I error is not strongly controlled among the DR-related analyses.

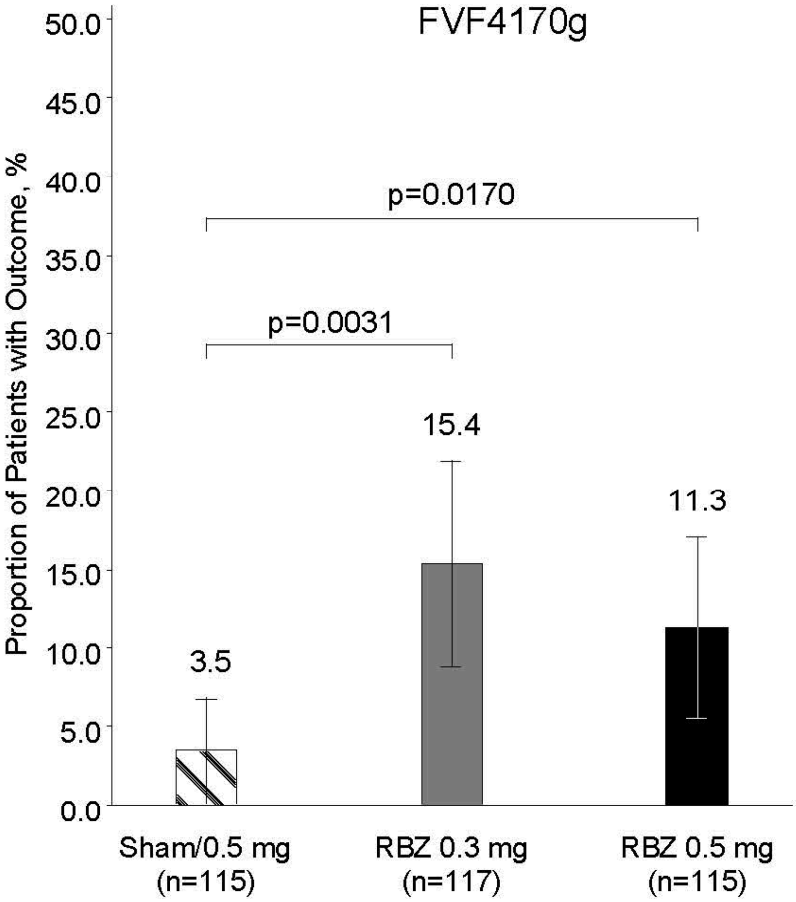
Proportion of subjects with a ≥ 3-step improvement from baseline in the ETDRS DR severity score at 36 months, as assessed by the central reading center using FP.

Table 6.1.2.5-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham / 0.5 mg RBZ n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=117
n (%)	4 (3.5%)	18 (15.4%)	13 (11.3%)
95% CI for percentage [a]	(0.1%, 6.8%)	(8.8%, 21.9%)	(5.5%, 17.1%)
Difference in % (vs. sham) [b]		11.4%	8.4%
95% CI of the difference [b]		(4.5%, 18.3%)	(2.2%, 14.6%)
p-value (vs. sham) [c]		0.0031	0.0170

Source: Module 5.3.5.3 ISE Table 13
Note: P-values are for testing difference between Ran bizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a By normal approximation of the observed proportions;
b Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

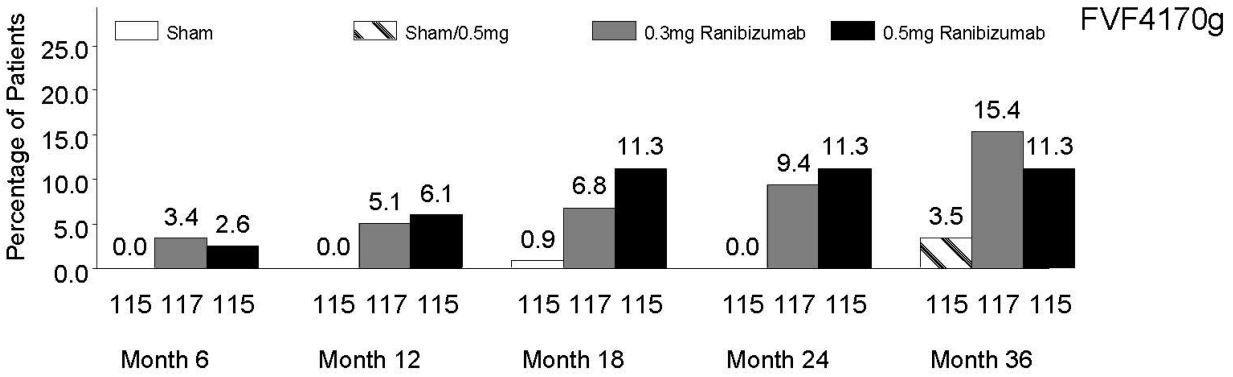
Figure 6.1.2.5-1
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 7
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Reviewer's Comment:
The proportion of subjects in the 0.3-mg and 0.5-mg ranibizumab groups who had a ≥ 3-step improvement from baseline in ETDRS DR severity score at Month 36 was 15% and 11%, respectively. When compared with the sham / 0.5-mg group, the differences were statistically significant with p-values, 0.0031 and 0.0170, for the 0.3-mg and 0.5-mg ranibizumab groups, respectively. Thus, the treatment group difference was maintained through Month 36.

Figure 6.1.2.5-2
Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 9

Reviewer's Comment:
The proportion of subjects with a ≥ 3-step improvement from baseline in ETDRS DR Severity Score in the study eye was greater in the ranibizumab treatment groups beginning at Month 6 and maintained through Month 36.

The percentage of subjects with a ≥ 3-step improvement from baseline in ETDRS DR Severity Score in the Sham/0.5 mg crossover group increased slightly by Month 36.

Proportion of subjects with a ≥ 2-step improvement from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP

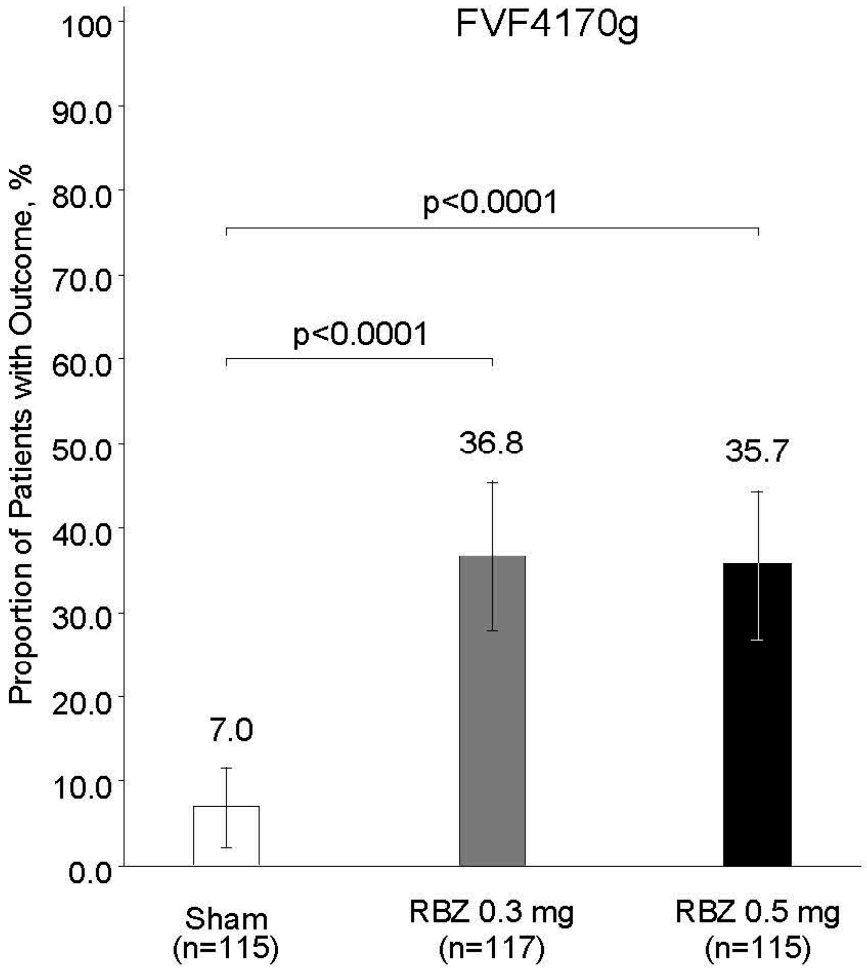
Table 6.1.2.5-2 Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Subjects with a Valid Score at Baseline; LOCF)

	Sham[a] / 0.5mg RBZ n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=115
Month 24			
n (%)	8 (7.0%)	43 (36.8%)	41 (35.7%)
95% CI for percentage [a]	(2.3%, 11.6%)	(28.0%, 45.5%)	(26.9%, 44.4%)
Difference in % (vs. sham) [b]		30.5%	28.3%
95% CI of the difference [b]		(20.9%, 40.2%)	(18.9%, 37.7%)
p-value (vs. sham) [c]		<0.0001	<0.0001
	Sham[a] / 0.5mg RBZ n=115	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=115**
Month 36			
n (%)	28 (24.3%)	45 (38.5%)	47 (40.9%)
95% CI for percentage [a]	(16.5%, 32.2%)	(29.6%, 47.3%)	(31.9%, 49.9%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		14.9%	17.6%
95% CI of the difference [b]		(3.6%, 26.2%)	(6.5%, 28.8%)
p-value (vs. sham) [c]		0.0134	0.0053

Source: Module 5.3.5.3 ISE Table 14
Note: P-values are for testing difference between Ran bizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

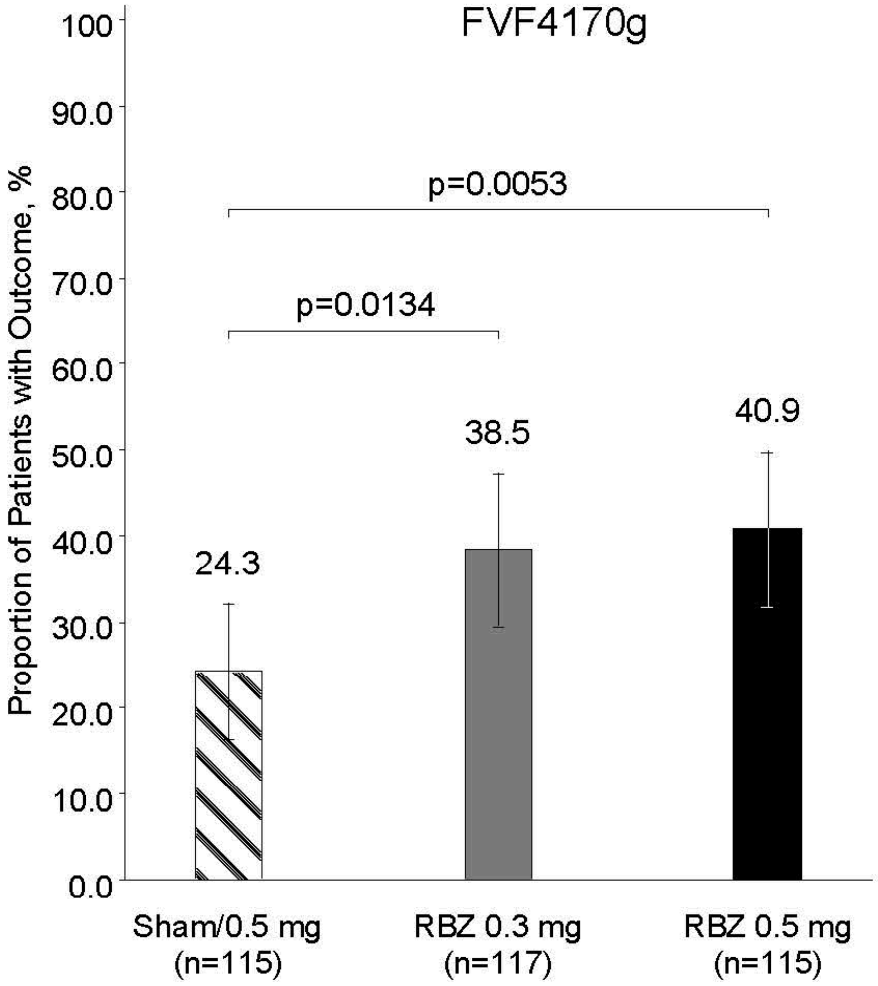
Reviewer's Comment:
At Month 24, a ≥ 2-step improvement in ETDRS DR severity score in the study eye was seen in 37% and 36% of patients in the ranibizumab 0.3-mg and 0.5-mg treatment groups respectively compared to 7% in the sham treatment group. The treatment group differences were statistically significant at p<0.0001 for both groups. The treatment group difference compared to sham/0.5-mg RBZ continued at Month 36, p=0.0134 and p=0.0053 levels for the ranibizumab 0.3-mg and 0.5-mg groups.

Figure 6.1.2.5-3
Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



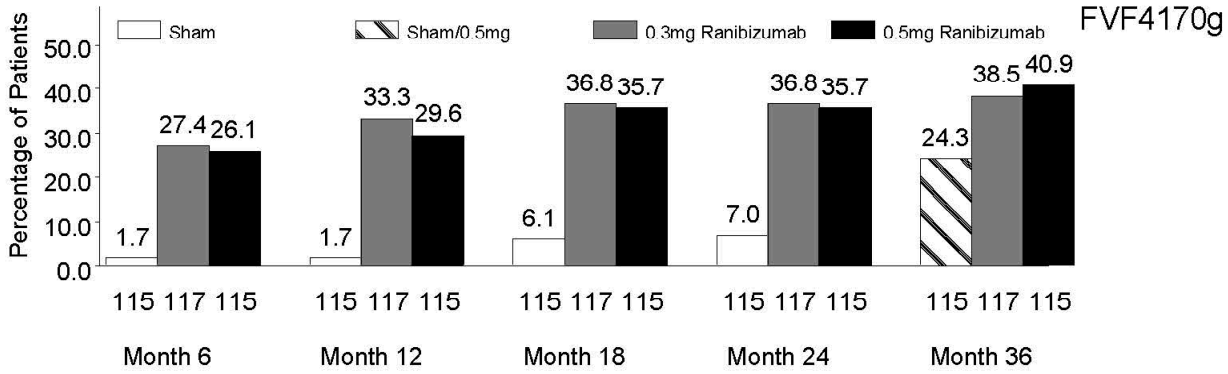
Source: Module 5.3.5.3 ISE Figure 10
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-4
Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 11
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-5
Proportion of Subjects with ≥ 2-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 13

Reviewer's Comment:
The proportion of subjects with a ≥ 2 -step improvement from baseline in ETDRS DR Severity Score in the study eye was greater in the ranibizumab treatment groups beginning at Month 6 and statistically significant and maintained through Month 36.

The proportion of subjects who achieved the lower threshold of ≥ 2-step improvement from baseline in ETDRS DR severity score in the study eye was greater in all treatment groups from Month 6 – Month 36. There was a relatively greater increase in the proportion of sham/0.5 mg group subjects seen from Month 18 to Month 36.

Proportion of subjects with a ≥ 3-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP

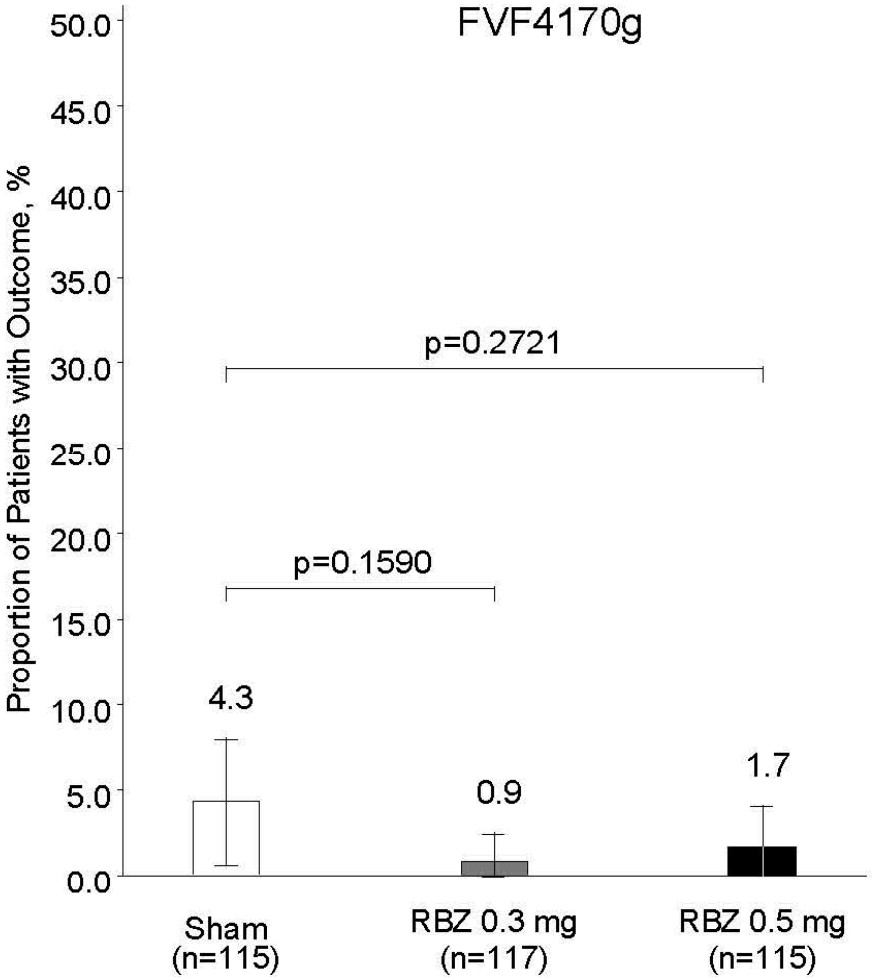
Table 6.1.2.5-3
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Subjects with a Valid Score at Baseline; LOCF)

	Sham[a] / 0.5 mg RBZ n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=115
Month 24			
n (%)	5 (4.3%)	1 (0.9%)	2 (1.7%)
95% CI for percentage [a]	(0.6%, 8.1%)	(0.0%, 2.5%)	(0.0%, 4.1%)
Difference in % (vs. sham) [b]		-3.0%	-2.5%
95% CI of the difference [b]		(-6.7%, 0.7%)	(-6.5%, 1.4%)
p-value (vs. sham) [c]		0.1590	0.2721
	Sham[a] / 0.5 mg RBZ n=115	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=115**
Month 36			
n (%)	5 (4.3%)	2 (1.7%)	2 (1.7%)
95% CI for percentage [a]	(0.6%, 8.1%)	(0.0%, 4.1%)	(0.0%, 4.1%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		-2.4%	-2.3%
95% CI of the difference [b]		(-6.5%, 1.6%)	(-6.6%, 1.9%)
p-value (vs. sham) [c]		0.2917	0.3101

Source: Module 5.3.5.3 ISE Table 15
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

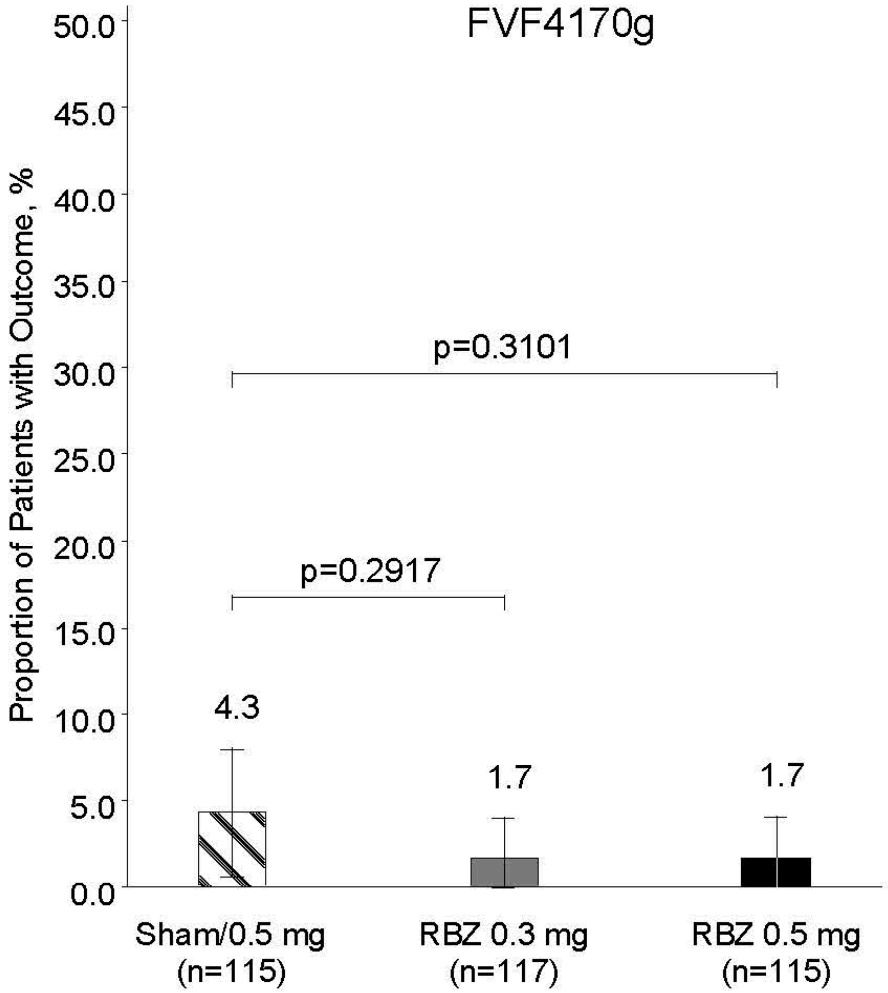
Reviewer's Comment:
Though numerically fewer subjects experienced a three-step or greater worsening from baseline in ETDRS Diabetic Retinopathy Severity score in the ranibizumab groups compared to sham at 24 months and sham/0.5-mg RBZ at 36 months, the differences were not statistically significant for any of the treatment group comparisons.

Figure 6.1.2.5-6
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



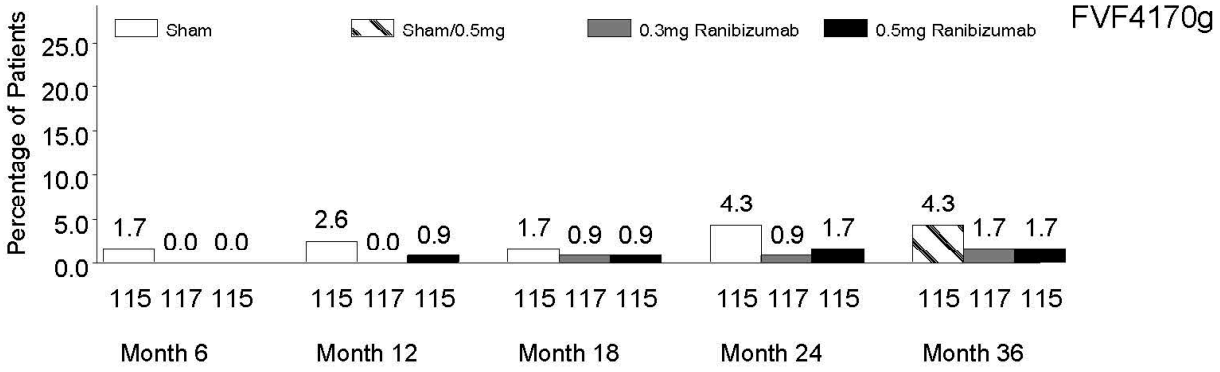
Source: Module 5.3.5.3 ISE Figure 14
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-7
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 15
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-8
Proportion of Subjects with ≥ 3-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 17

Reviewer's Comment:

The proportion of subjects with worsening DR throughout the study was highest in the sham and sham/0.5-mg ranibizumab group.

Proportion of subjects with a ≥ 2-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP

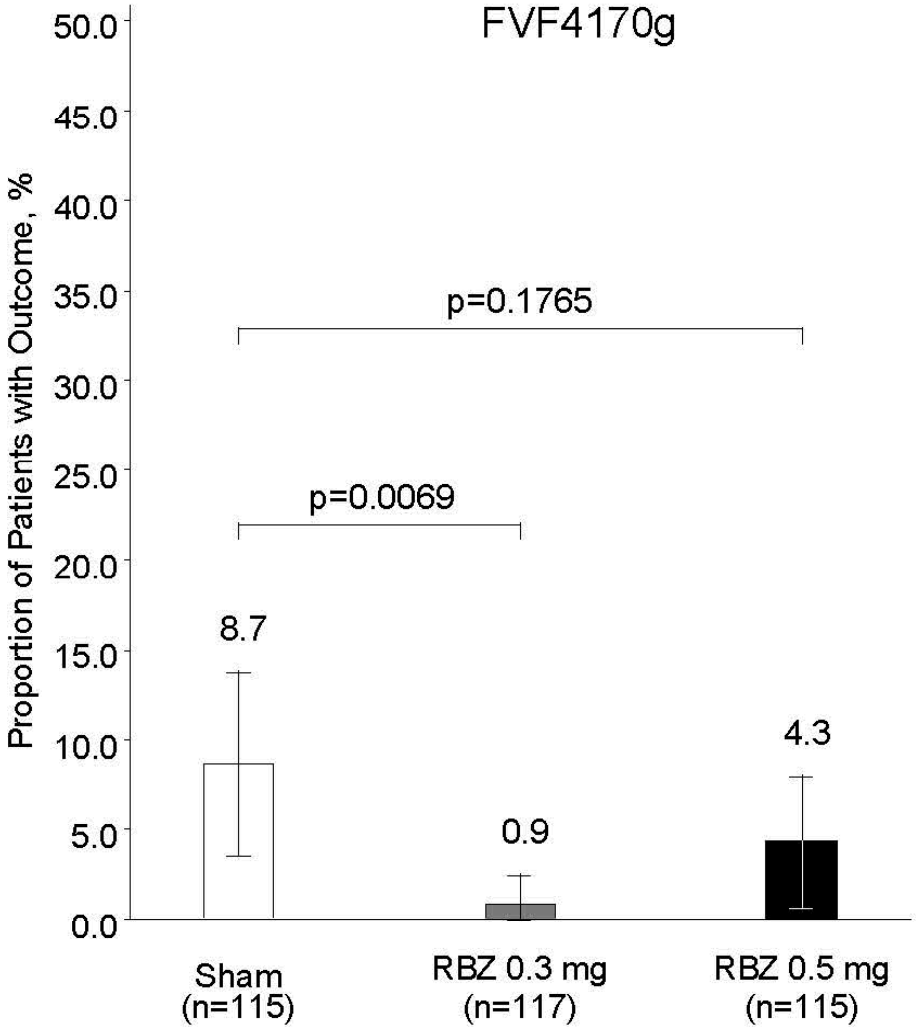
Table 6.1.2.5-4
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 and Month 36 (Randomized Subjects with a Valid Score at Baseline; LOCF)

	Sham[a] / 0.5 mg RBZ n=115	0.3 mg RBZ n=117	0.5 mg RBZ n=115
Month 24			
n (%)	10 (8.7%)	1 (0.9%)	5 (4.3%)
95% CI for percentage [a]	(3.5%, 13.8%)	(0.0%, 2.5%)	(0.6%, 8.1%)
Difference in % (vs. sham) [b]		-7.7%	-4.5%
95% CI of the difference [b]		(-13.0%, -2.4%)	(-10.6%, 1.6%)
p-value (vs. sham) [c]		0.0069	0.1765
	Sham[a] / 0.5 mg RBZ n=115	**0.3 mg RBZ n=117**	**0.5 mg RBZ n=115**
Month 36			
n (%)	11 (9.6%)	5 (4.3%)	5 (4.3%)
95% CI for percentage [a]	(4.2%, 14.9%)	(0.6%, 7.9%)	(0.6%, 8.1%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		-5.5%	-5.5%
95% CI of the difference [b]		(-11.9%, 1.0%)	(-11.9%, 1.0%)
p-value (vs. sham) [c]		0.1075	0.1085

Source: Module 5.3.5.3 ISE Table 16
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

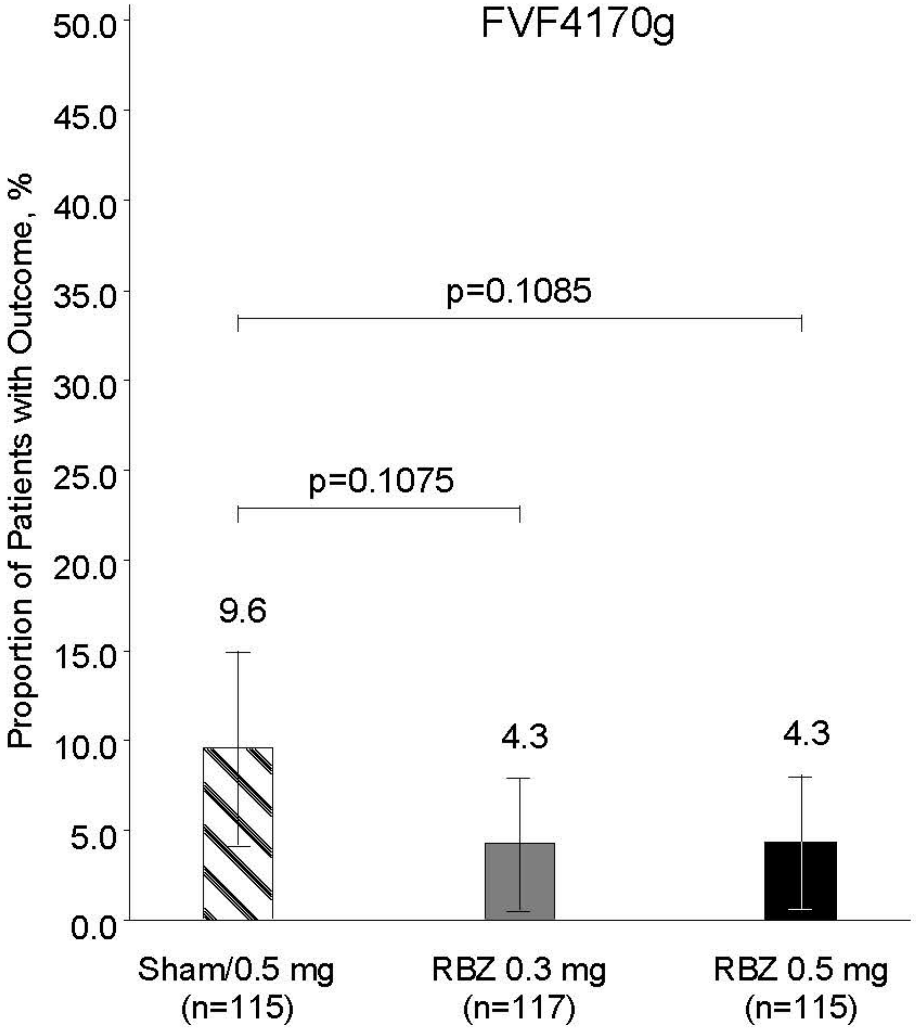
Reviewer's Comment:
Fewer subjects experienced a 2-step or greater worsening from baseline in ETDRS Diabetic Retinopathy Severity Level in the ranibizumab groups compared to sham at 24 and 36 months. The treatment group difference was only statistically significant for the ranibizumab 0.3 mg group compared to sham and Month 24.

Figure 6.1.2.5-9
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24
(Randomized Subjects with a Valid Score at Baseline; LOCF)



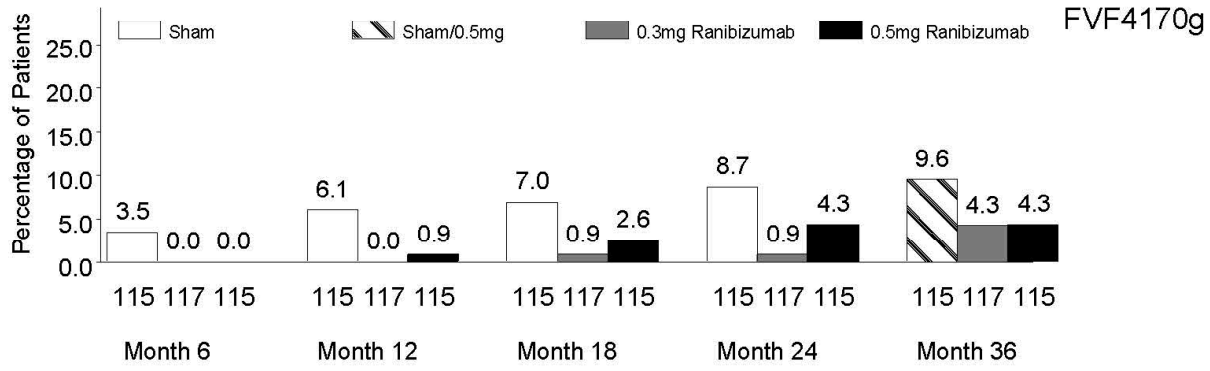
Source: Module 5.3.5.3 ISE Figure 18
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-10
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye at Month 36
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 19
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-11
Proportion of Subjects with ≥ 2-Step Worsening from Baseline in ETDRS DR Severity Score in the Study Eye Over Time
(Randomized Subjects with a Valid Score at Baseline; LOCF)



Source: Module 5.3.5.3 ISE Figure 21

Reviewer's Comment:

The proportion of subjects with worsening DR throughout the study was highest in the sham and sham/0.5-mg ranibizumab group. The proportion of subjects increased in all treatment groups at Month 36.

Proportion of subjects progressing to PDR as determined by the indirect ophthalmoscopy assessment of the presence of neovascularization on the optic disc, elsewhere on the retina, or iris by Month 24 and 36.

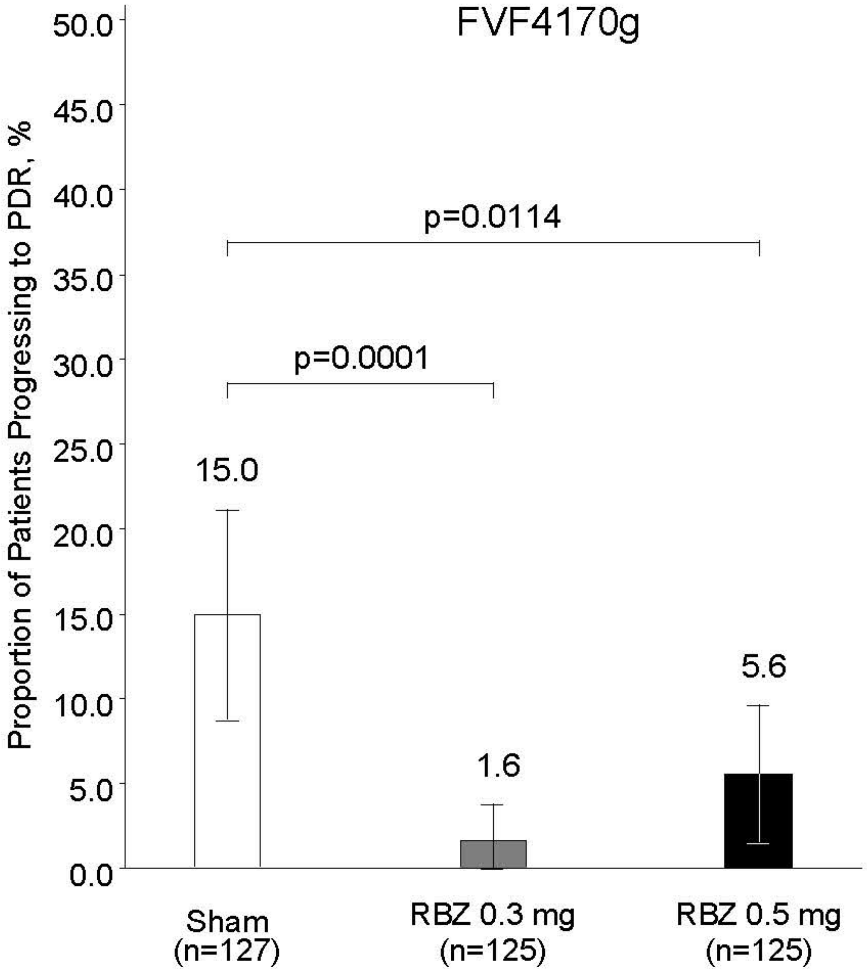
Table 6.1.2.5-5
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye at Month 24 and Month 36 (Study FVF4170g)

	Sham[a] / 0.5 mg RBZ n=127	0.3 mg RBZ n=125	0.5 mg RBZ n=125
Month 24			
n (%)	19 (15.0%)	2 (1.6%)	7 (5.6%)
95% CI for percentage [a]	(8.8%, 21.2%)	(0.0%, 3.8%)	(1.6%, 9.6%)
Difference in % (vs. sham) [b]		-13.6%	-9.8%
95% CI of the difference [b]		(-20.2%, -7.0%)	(-17.0%, -2.6%)
p-value (vs. sham) [c]		0.0001	0.0114
	Sham[a] / 0.5 mg RBZ n=127	**0.3 mg RBZ n=125**	**0.5 mg RBZ n=125**
Month 36			
n (%)	22 (17.3%)	3 (2.4%)	9 (7.2%)
95% CI for percentage [a]	(10.7%, 23.9%)	(0.0%, 5.1%)	(2.7%, 11.7%)
Difference in % (vs. sham/0.5 mg RBZ) [b]		-15.6%	-10.6%
95% CI of the difference [b]		(-22.7%, -8.4%)	(-18.6%, -2.5%)
p-value (vs. sham) [c]		<0.001	0.0119

Source: Module 5.3.5.3 ISE Table 17
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no).
a For 24 month outcomes, data in this column represent the sham group. For 36-month outcomes, data in this column represent the sham/0.5 mg crossover group.
b By normal approximation of the observed proportions;
c Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates. The last observation carried forward imputation method was used.

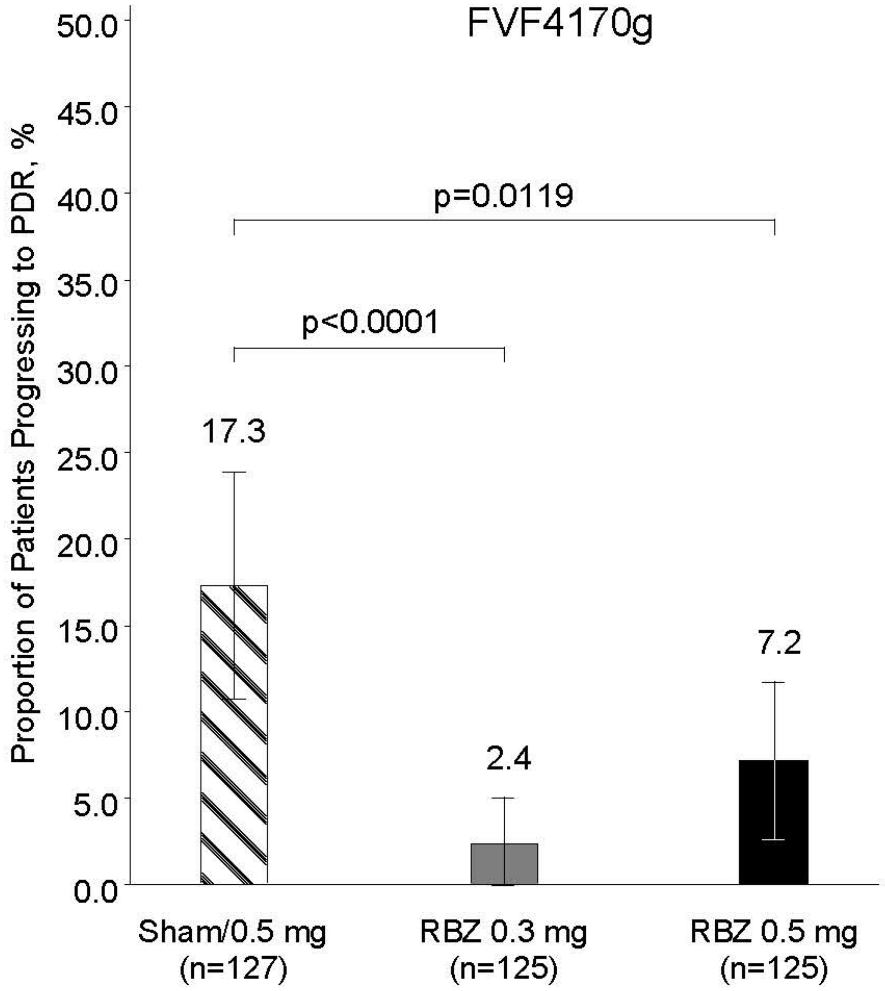
Reviewer's Comment:
The proportion of subjects who progressed to PDR in the ranibizumab groups compared to sham and sham/0.5-mg RBZ treatment groups at Month 24 and Month 36 was smaller and statistically significantly so for each of the four comparisons.

Figure 6.1.2.5-12
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye at Month 24



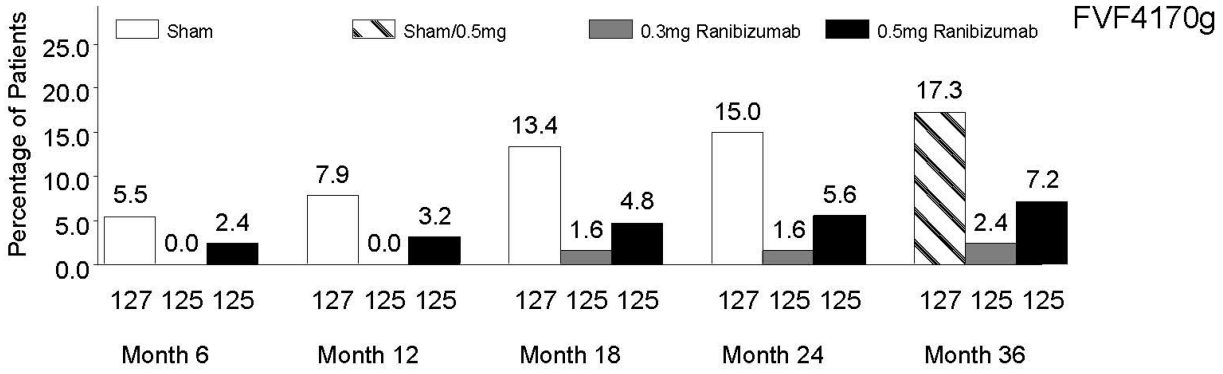
Source: Module 5.3.5.3 ISE Figure 22
Note: P-values are for testing difference between Ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-13
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye at Month 36



Source: Module 5.3.5.3 ISE Figure 23
Note: P-values are for testing difference between ranibizumab groups and sham or sham/0.5 mg group. Results were obtained using the CMH chi-square test, with adjustment for stratification factors. Strata were defined using baseline BCVA score (≤55, > 55 letters), baseline HbA1c (≤ 8%, >8%), and prior therapy for DME in the study eye (yes, no). P-values are not adjusted for multiplicity. Vertical bars are 95% confidence interval.

Figure 6.1.2.5-14
Proportion of Subjects Progressing to Proliferative Diabetic Retinopathy in the Study Eye Over Time



Source: Module 5.3.5.3 ISE Figure 25

Reviewer's Comment:
The proportion of subjects who progressed to PDR in the ranibizumab groups compared to sham and sham/0.5-mg RBZ treatment groups at Month 24 and Month 36 was smaller and statistically significantly so for each of the four comparisons. From Month 24 through Month 36, the proportion of subjects who progressed to PDR increased in each treatment group.

6.1.2.6 Other Endpoints
None.

6.1.2.7 Subpopulations

Demographic data, diagnoses, and baseline lesion characteristics between treatment groups within each study were comparable.

The number of patients within any particular 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.

Diabetic retinopathy is a disease seen only in adults; therefore, no pediatric trials were conducted for this drug product.

6.1.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant performed adequate dose ranging studies during the drug development program. Lucentis (ranibizumab) 0.3-mg and 0.5-mg dose have been demonstrated to be safe and effective in two Phase 3 clinical trials for the proposed indication. Studies

have not been powered to determine a difference between the doses. The frequency of dosing needed is not well established.

6.1.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Reviewer's Comment:
No evidence of tolerance or withdrawal effects has been detected in any trials submitted in the original BLA 125156 for Lucentis (ranibizumab injection) or subsequent supplements.

6.1.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy or analysis issues.

7 Review of Safety

No new safety data are presented in this submission.

7.1 Methods

No new safety data was presented in this submission.

7.2 Adequacy of Safety Assessments

No new safety data was presented in this submission.

7.3 Major Safety Results

No new safety data was presented in this submission.

7.4 Supportive Safety Results

No new safety data was presented in this submission.

7.5 Other Safety Explorations

No new safety data was presented in this submission.

7.6 Additional Safety Evaluations

No new safety data was presented in this submission.

7.7 Additional Submissions / Safety Issues

The 4 month Safety Update was submitted on November 5, 2014. This safety update contains no new data due to the following:

- This supplement is based on efficacy data from studies FVF4168g and FVF4170g. No safety data was submitted in support of sBLA 125156/105.

- Studies FVF4168g and FVF4170g were completed before submission of BL 125156/106. Final CSRs for these trials were submitted to the license on 27 January 2014 (STN: BL 125156/ Sequence Number 0103).

- There are no on-going clinical trials with ranibizumab being conducted under Genentech's ranibizumab BB-IND 8633.

8 Postmarket 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.

9 Appendices

9.1 Literature Review/References

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.

9.2 Advisory Committee Meeting

An Advisory Committee was not held regarding this application.

9.3 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA 125156 / S-106

Submission Date(s): August 7, 2014

Applicant: Genetech, Inc.

Product: Lucentis (ranibizumab) injection, 0.3 mg

Reviewer: Rhea A. Lloyd, MD

Date of Review: October 30, 2014

Covered Clinical Study (Name and/or Number):
FVF4168g and FVF4170g.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Study FVF4168g: 391 investigators Study FVF4170g: 416 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Study FVF4168g: 3 Study FVF4170g: 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: Five Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: One		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[5] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

In support of this sBLA, Genentech, Inc. has evaluated all new and updated financial disclosure information obtained since the DME sBLA submission. Studies FVF4168g and FVF4170g are now concluded, and all study sites are closed. At the time of site closure for each center, financial disclosure information was verified, and investigators were notified of their obligation to report any updates to their financial disclosure information for an additional year.

Genentech abides by a due diligence policy to attempt to obtain financial disclosure information for those investigators for whom a signed financial disclosure form was not received. Unless an investigator left the study site without providing forwarding information, Genentech makes multiple contact attempts via email, fax, phone, and/or letter in its efforts to obtain the outstanding information. No further follow-up is planned, as these studies are now closed and more than a year has elapsed since their completion.

The Table below provides a summary of the collected information and findings provided in

5 See [web address].

the DME sBLA. No additional risk of bias was identified since no new positive disclosures have been reported.

Genentech minimized potential bias of clinical study results by any of the investigators in that the study was multicenter, randomized, double-masked and sham-injection controlled through Month 24.

Genentech has determined there were financial interests or arrangements to disclose from the following investigators:

Study Protocol Number	Clinical Site Number	Number of Patients Enrolled at Site (b) (6)	Investigator Name	Disclosure	Genentech FD form	Genentech/ Roche FD form
FVF4168g			David Brown [a]	Consulting fees and honorarium of approximately $55,000		X
FVF4168g			Larry Singerman [a]	Investigator sponsored research grant for $250,000 reported on Roche/Genentech financial disclosure form signed 8/15/2011. Original Genentech financial disclosure form signed 5/9/2007 indicated no financial disclosures at that time.		X
FVF4168g			Barry Taney [a]	600 shares of Genentech stock. From the time that patients were first enrolled in either Study FVF4168g or FVF4170g to Roche's acquisition of Genentech on 3/26/2009, Genentech's stock price did not close above $100/share. Therefore it is estimated that 600 shares of Genentech stock would have had a maximum value of $60,000 until the time of Roche's acquisition of Genentech.		X
FVF4170g			David Brown [a]	Received consulting fees and honorarium of approximately $55,000.		X
FVF4170g			Michael Cooney [b]	$25,000 in speaker fees and/or honorarium		X
FVF4170g			Howard Fine [b]	Approximately $22,000 in speakers fee and/or honorarium and approximately $3000 in consulting fees		X
FVF4170g			David Richards [b]	In-house unrestricted research grant of $50,000	X	

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

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/s/

RHEA A LLOYD
01/28/2015

WILLIAM M BOYD
01/29/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:	Applicant:	Stamp Date:
sBLA 125156/ 106	Genentech, Inc.	August 7, 2014
Drug Name: Lucentis (ranibizumab injection)	NDA/BLA Type: Efficacy Supplement	

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			X	The studies were previously reviewed in Supplement S-076 which was approved on August 10, 2012. New clinical data analyses for (b) (4) [redacted] a labeling change.
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: FVF4168g Indication: Treatment of diabetic macular edema (DME) Pivotal Study #2: FVF4170g Indication: Treatment of diabetic macular edema (DME)	X			The studies were previously reviewed in Supplement S-076 which was approved on August 10, 2012. New clinical data analyses for (b) (4) [redacted] labeling change.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
	SAFETY				
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	The studies were previously reviewed in Supplement S-076 which was approved on August 10, 2012. New clinical data analyses for (b) (4) [redacted] labeling change.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
	OTHER STUDIES				
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
	PEDIATRIC USE				
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
	ABUSE LIABILITY				
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
	FOREIGN STUDIES				
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
	DATASETS				
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
	CASE REPORT FORMS				
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Submitted with S-076 which was approved August 10, 2012.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
	FINANCIAL DISCLOSURE				

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
38.	Has the applicant submitted the required Financial Disclosure information?	X			Submitted with S-076 which was approved August 10, 2012.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Submitted with S-076 which was approved August 10, 2012.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No potential filing issues have been identified.

Rhea A. Lloyd, MD — 09/15/2014

Reviewing Medical Officer — Date

William M. Boyd, MD — 09/15/2014

Clinical Team Leader — Date

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/s/

RHEA A LLOYD
09/15/2014

WILLIAM M BOYD
09/16/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

CHEMISTRY REVIEW(S)

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR BLA/NDA Supplements (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125156/106	Genentech	07-Aug-14
Established/Proper Name:	**BLA/NDA Type:**	
Lucentis® /ranibizumab	BLA	

Brief description of the change:	Revision of the Lucentis USPI to include a new indication for the treatment of patients with (b) (4)
Reviewer:	Chen Sun
Office/Division:	OBP/DMA

On **initial** overview of the BLA/NDA **supplement** for filing:

The following was submitted in support of the change (check all that apply):

x	A detailed description of the proposed change
x	Identification of the product(s) involved
	A description of the manufacturing site(s) or area(s) affected
	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
	The data derived from such studies
	Relevant validation protocols and data
	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues):

IS THE PRODUCT QUALITY SECTION OF THE SUPPLEMENT FILEABLE? Yes

If the supplement is not fileable from the product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

CHEN SUN
10/20/2014

MICHELE K DOUGHERTY
10/20/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

ENVIRONMENTAL ASSESSMENT

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

Office of Biotechnology Products
Division of Monoclonal Antibodies
Rockville, MD 20852
Tel. 301-827-0850

Memorandum of Review

Date: November 22, 2014

From: Chen Sun, M.D., Ph.D., DMA, OBP, OPS, CDER

Through: Michele Dougherty, Ph.D., Team Leader, DMA, OBP, OPS, CDER

Subject: STN: 125156.106: Revision of the Lucentis U.S. Prescribing Information (USPI) to include a new indication (b) (4)

Applicant: Genentech Inc

Product: ranibizumab (Lucentis)

Contact: Clara Cambon, Pharm. D.
Regulatory Program Management

Submitted: August 7, 2014

Action Due Date: February 6, 2015

Review Recommendation: I recommend approval of Genentech's request regarding the categorical exclusion from an Environmental Assessment.

1. FDA Regional Information
1.12. Other Correspondence
1.12.14. Environmental Analysis

Genentech is requesting a categorical exclusion from an Environmental Assessment in accordance with the criteria set forth in 21CFR §25.15 (d) and 25.31 (c). The Sponsor claims that this supplement to a marketing approval of a biologic product meets the criteria for substances that occur naturally in the environment when the action does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment per 21 CFR §25.31(c).

Reviewer comment: *There is no information in this supplement indicating that any additional environmental information is warranted. The Sponsor's request regarding the categorical exclusion from an Environmental Assessment is acceptable.*

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/s/

CHEN SUN
10/29/2014

MICHELE K DOUGHERTY
10/29/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125156/106 **Applicant: Genentech Inc** **Stamp Date: 8-7-2014**

Drug Name: Lucentis® **BLA Type: Supplemental (Efficacy)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		There are no changes to the nonclinical sections of the approved label.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? *Yes*

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

No nonclinical studies were submitted with this supplemental BLA. There are no nonclinical changes to the approved label. There are no changes to the approved dosage recommendations. There are no nonclinical filing issues.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Maria I Rivera, PhD

Reviewing Pharmacologist Date

Lori E Kotch, PhD

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

MARIA I RIVERA
01/21/2015

LORI E KOTCH
01/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	BLA 125156/S-106
Supporting document/s:	635
Applicant's letter date:	8-7-14
CDER stamp date:	8-7-14
Product:	Lucentis (Ranibizumab injection)
Indication:	(b) (4)
Applicant:	Genentech, Inc
Review Division:	Transplant and Ophthalmology Product
Reviewer:	María I Rivera. PhD
Supervisor/Team Leader:	Lori E Kotch, PhD
Division Director:	Renata Albrecht, MD
Project Manager:	Christina Marshall

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125156/S-106 are owned by Genentech or are data for which Genentech has obtained a written right of reference. Any information or data necessary for approval of BLA 125156/S-106 that Genentech does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 125156/S-106.

The purpose of this supplemental BLA is to support a revision of the LUCENTIS® USPI to include a new indication [redacted] (b) (4) (DR). The proposed USPI revisions are based on the safety and efficacy results from clinical Study FVF4168g and clinical Study FVF4170g in patients with diabetic macular edema (DME). All enrolled subjects in Studies FVF4168g and FVF4170g had DME and DR at baseline. Patients received monthly injections of LUCENTIS® (0.3 or 0.5 mg) for 12 to 36 months. The sponsor claims that subjects treated with LUCENTIS® demonstrated [redacted] (b) (4)

The intended dose for LUCENTIS® [redacted] (b) (4) is 0.3 mg (0.05 mL) administered by intravitreal injection once a month. This dosing regimen is identical to that previously approved by the FDA for the treatment of DME. No new nonclinical studies were submitted with this supplemental BLA. There are no revisions to the nonclinical sections of the previously approved label. As such, there are no new concerns/recommendations from the nonclinical perspective.

CC list:

C. Marshall/PM
R. Lloyd/MO

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/s/

MARIA I RIVERA
01/14/2015

LORI E KOTCH
01/14/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

STATISTICAL REVIEW(S)

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

SECONDARY REVIEW

NDA/BLA #:	BLA 125156/S-106
Drug Name:	Lucentis® (ranibizumab intravitreal injection) 0.3 mg monthly
Proposed Indication:	(b) (4)
Applicant:	Genentech, Inc.
Date(s):	Stamp date: August 7, 2014
	PDUFA date: February 7, 2015
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
Statistical reviewer:	Dongliang Zhuang, Ph.D.
Secondary reviewer	Yan Wang, Ph.D.
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Medical reviewer: Rhea Lloyd, M.D.
	Clinical team leader: William Boyd, M.D.
	Deputy Division Director: Wiley Chambers, M.D.
	Division Director: Renata Albrecht, M.D.
Project Manager:	Christina Marshall. M.S.

Keywords: diabetic retinopathy (DR) , diabetic macular edema (DME), best-corrected visual acuity (BCVA), diabetic retinopathy severity score, Early Treatment Diabetic Retinopathy Study (ETDRS)

Table of Contents

LIST OF TABLES

1 CONCLUSION AND RECOMMENDATION

Genentech, the applicant, has submitted two studies in this supplemental BLA125156/S-106 to support a proposed new labeling [redacted] for Lucentis 0.3 mg. There are two issues related to this application that I will address in this review. The first is regarding the statistical evidence provided in this submission. The two studies, FVF4168g and FVF4170g (referred as Studies D-1 and D-2), were previously submitted and used to support the approval of the indication of treatment of diabetic macular edema (DME) on August 10, 2012. As outlined in the next section, I agree with the primary statistical reviewer's conclusion that Studies D-1 and D-2 demonstrated efficacy of Lucentis 0.3 mg in the treatment of DR for patients with DME. The second issue is regarding how this information should be included in the labeling. The applicant proposed to include [redacted] However, because only subjects with DME were enrolled in Studies D-1 and D-2, the efficacy results from these two studies do not completely support the applicant's proposed [redacted]. Though the details of how the information regarding [redacted] is described in the labeling are deferred to the medical division, I have the following two recommendations:

1. [redacted]
2. Include a new indication "treatment of DR in patients with DME" in the labeling along with efficacy results in the CLINICAL STUDIES section.

[redacted] This recommendation is consistent with how we usually handle other secondary/supportive endpoints.

For the second option, it is not clear to me whether including the new indication will provide additional information beyond what the first option will provide in terms of helping healthcare professionals to prescribe Lucentis appropriately. To address this question, clinical input is needed.

[redacted] I agree with the primary statistical reviewer's recommendation. We recommend that the labeling include the results of ≥2-step and ≥3-step improvement endpoint [redacted] However, without providing a justification, the applicant proposed to include [redacted] the results of ≥2-step and ≥3-step improvement endpoints in the labeling. It appears that the applicant's selection of these two endpoints is driven by the seemingly better results (i.e. smaller p-values for treatment comparison shown in Table 3) of the improvement endpoints [redacted] This apporach is not justifiable from a statistical perspective as discussed further below.

(b) (4)

2 STATISTICAL ISSUES

There is no major statistical concern identified in the primary statistical review and in my review. The key efficacy analyses included in this application are based on the following four endpoints:

- ≥2-step improvement from baseline in the DR severity score at 24 months
- ≥3-step improvement from baseline in the DR severity score at 24 months
- ≥2-step progression from baseline in the DR severity score at 24 months
- ≥3-step progression from baseline in the DR severity score at 24 months.

Although only the last endpoint (i.e., ≥3-step progression) was pre-specified as a key secondary endpoint in the study protocol, these four endpoints are all derived from the DR severity score at baseline and 24 months; thus they are closely related and capture the treatment effect on DR from different perspectives. Additionally, the ophthalmic clinical team considers these endpoints clinicaly relevant for the (b) (4)

2.1 Pre-defined efficacy endpoints and testing procedure to control Type I error in Studies D-1 and D-2

The pre-defined primary efficacy endpoint in Studies D-1 and D-2 was for the DME indication and defined as the proportion of subjects who gained at least 15 letters in best-corrected visual acuity (BCVA) at 24 months from baseline. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for the two treatment comparisons: sham vs. 0.3-mg Lucentis and sham vs. 0.5-mg Lucentis.

Contingent upon statistical significance in the primary efficacy endpoint for a given Lucentis dose group, the following three categories of key secondary efficacy endpoints were compared between this dose group and the sham group separately at an overall 0.05 significance level. Within each category, the testing was performed in the order listed below. If one test in a given category was not positive, then all the subsequent tests within that category would not be considered positive regardless of the associated p-values.

A. Visual acuity endpoints:
   1. Mean change from baseline in BCVA at 24 months
   2. Proportion of subjects with a BCVA Snellen equivalent of 20/40 or better at 24 months
   3. Mean change from baseline in BCVA at 24 months in subjects with focal edema at baseline
   4. Proportion of subjects who lost <15 letters in BCVA at 24 months compared to baseline

B. Mean number of macular laser treatments during 24 months

C. Anatomic efficacy endpoints:
   1. Mean change from baseline in central foveal thickness at 24 months
   2. Proportion of subjects with a ≥3-step progression from baseline in the DR severity score at 24 months
   3. Proportion of subjects with resolution of leakage at 24 months

The endpoints of ≥2-step improvement and ≥2-step progression from baseline in the DR severity score at 24 months were defined as exploratory efficacy endpoints in the applicant's statistical analysis plan and the clinical study report (CSR). In the supplemental BLA submission for the DME indication, the applicant proposed (b) (4) (EDR location: \\CDSESUB1\evsprod\BLA125156\0034\m1):

(b) (4)

(b) (4) The results of this endpoint were included in the applicant's briefing meeting document for the pre-sBLA meeting scheduled on May 20, 2014. In the current application, the applicant stated that the analysis of ≥3-step improvement was the main analysis to support their proposed (b) (4)

2.2 My interpretation of the analysis results of the endpoint of ≥3-step progression from baseline in the DR severity score at 24 months

The p-values for the treatment comparisons for the pre-defined endpoints are presented in Table 2. For the comparison between the sham and 0.3-mg Lucentis groups, the p-values were all below 0.05 for all the pre-defined endpoints except for the endpoint of ≥3-step progression from baseline in the DR severity score at 24 months (row C2, highlighted in Table 2).

Table 2: P-values for Treatment Comparison of the Pre-defined Endpoints at Month 24

	Study D-1		Study D-2	
Endpoint	**Sham vs Lucentis 0.3 mg**	**Sham vs Lucentis 0.5 mg**	**Sham vs Lucentis 0.3 mg**	**Sham vs Lucentis 0.5 mg**
Primary	<0.0001	<0.0001	<0.0001	0.0002
A1	<0.0001	<0.0001	<0.0001	<0.0001
A2	0.0002	<0.0001	<0.0001	<0.0001
A3	0.0102	0.0005	0.0005	0.0011
A4	0.0119	0.1384	0.0086	0.0126
B	<0.0001	<0.0001	<0.0001	<0.0001
C1	<0.0001	<0.0001	<0.0001	<0.0001
C2 (≥3-step progression)	**0.0853**	0.0073	**0.1590**	0.2721
C3	0.0002	<0.0001	<0.0001	<0.0001

Source: Applicant's CSRs for the DME indication (EDR location: \\CDSESUB1\evsprod\BLA125156\0034\m5).

The detailed results of the endpoint of ≥3-step progression from baseline are presented in Table 3. Although not statistically significant, compared to the sham group, the Lucentis groups had approximately 2% to 6% fewer subjects who progressed by ≥3-step from baseline in the two studies. In Study D-1, the proportion of subjects with a ≥3-step progression was 6% in the sham group, 2% in the 0.3-mg Lucentis group, and 0% in the 0.5-mg Lucentis group; the treatment difference was: -4% [95% CI: (-9%, 1%), p-value =0.0853] for 0.3 mg vs. sham, and -6% [95% CI: (-10%, -2%), p-value =0.0073] for 0.5 mg vs. sham. In Study D-2, the proportion of subjects with a ≥3-step progression was 4% in the sham group, 1% in the 0.3-mg Lucentis group, and 2% in the 0.5-mg Lucentis group; the treatment difference was: -3% [95% CI: (-7%, 1%), p-value =0.1590] for 0.3 mg vs. sham, and -3% [95% CI: (-7%, 2%), p-value =0.2721] for 0.5 mg vs. sham.

To further elucidate the treatment effect based on the DR severity score data, the applicant analyzed the endpoints of ≥2-step progression, ≥2-step improvement, and ≥3-step improvement from baseline. The results are positive for all three endpoints and show significant treatment benefit of Lucentis on the improvement of DR severity score (see Table 3). For example, compared to the sham-treated subjects, the Lucentis-treated subjects were more likely to improve by ≥2-step in both studies. For Study D-1, the proportion of subjects with a ≥2-step improvement was 4% in the sham group, 39% in the 0.3-mg Lucentis group, and 36% in the 0.5-mg Lucentis group; the treatment difference was: 35% [95% CI: (26%, 44%), p-value <0.0001] for 0.3 mg vs. sham, and 32% [95% CI: (23%, 41%), p-value <0.0001] for 0.5 mg vs. sham. For Study D-2, the proportion of subjects with a ≥2-step improvement was 7% in the sham group, 37% in the 0.3-mg Lucentis group, and 36% in the 0.5-mg Lucentis group; the treatment difference was: 31% [95% CI: (21%, 40%), p-value <0.0001] for 0.3 mg vs. sham, and 28% [95% CI: (19%, 38%), p-value <0.0001] for 0.5 mg vs. sham. Note: the p-values presented for the non-predefined endpoints in Table 3 should be considered as descriptive and not for hypothesis testing.

Table 3: Efficacy Results of Diabetic Retinopathy Severity Score at Month 24

Endpoint	Study[a]	Sham	0.3 mg	0.5 mg	Treatment Difference (95% CI)[b] p-value[b] 0.3 mg vs. Sham	0.5 mg vs. Sham
Improved ≥2-step from baseline	D-1	4%	39%	36%	35% (26%, 44%) <0.0001	32% (23%, 41%) <0.0001
	D-2	7%	37%	36%	31% (21%, 40%) <0.0001	28% (19%, 38%) <0.0001
Improved ≥3-step from baseline	D-1	2%	17%	18%	15% (7%, 22%) 0.0002	15% (8%, 22%) 0.0001
	D-2	0%	9%	11%	9% (4%, 14%) 0.0014	12% (6%, 17%) 0.0001
Progressed ≥2-step from baseline	D-1	11%	2%	0%	-9% (-14%, -3%) 0.0075	-11% (-16%, -5%) 0.0003
	D-2	9%	1%	4%	-8% (-13%, -2%) 0.0069	-5% (-11%, 2%) 0.1765
Progressed ≥3-step from baseline	D-1	6%	2%	0%	-4% (-9%, 1%) 0.0853	-6% (-10%, -2%) 0.0073
	D-2	4%	1%	2%	-3% (-7%, 1%) 0.1590	-2% (-7%, 1%) 0.2721

[a] Included randomized subjects who had gradable baseline DR severity score; D-1: Sham, n=124, 0.3 mg, n=117, 0.5 mg, n=119. D-2: Sham, n=115 and 0.3 mg, n=117, 0.5 mg, n=115.
[b] Adjusted estimate based on stratified model; LOCF was used to impute missing data.
Source: Tables 13, 14, 15, and 16 from the Applicant's Integrated Summary of Efficacy (EDR location: \\CDSESUB1\evsprod\BLA125156\0122\m5).

The positive results for the endpoints of ≥2-step improvement, ≥3-step improvement, ≥2-step progression, and ≥3-step progression, coupled with the statistically significant results on all other pre-defined endpoints and the plausible biological mechanism of action of Lucentis, provide substantial evidence of efficacy of Lucentis treatment for DR in patients with DME. In this case, the non-statistically significant positive results on the pre-defined endpoint of ≥3-step progression are not an indication of lack of treatment efficacy; instead, they reflect the low statistical power in demonstrating a treatment difference. It is noted that very few subjects (approximately 4% to 6%) in the sham groups had a ≥3-step progression at 24 months. Based on these low background rates and assuming Lucentis can reduce these rates by half, these two studies would have a power less than 30% to yield a statistically significant result for treatment comparisons.

Studies D-1 and D-2 were considered as positive studies based on the results of the pre-specified primary endpoint and consistent results on numerous secondary endpoints. Despite the lack of statistical significance on the one pre-defined DR secondary endpoint, we find the DR results in general very consistent across multiple definitions of the DR severity endpoint. If the medical division determines that inclusion of this information into the labeling is important for the prescribing physician, we strongly recommend that all the information provided in Table 1 be included and not limited to either (b) (4) or the two improvement endpoints (i.e., ≥2-step and ≥3-step improvement) as proposed by the applicant.

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/s/

YAN WANG
01/15/2015

DIONNE L PRICE
01/15/2015
Concur

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

NDA/BLA #:	BLA 125156
Supplement #:	S-106
Drug Name:	Lucentis® (ranibizumab intravitreal injection) 0.3 mg monthly
Indication(s):	(b) (4)
Applicant:	Genentech, Inc.
Date(s):	Submitted: August 7, 2014
	PDUFA Goal date: February 7, 2015
Review Priority:	Priority
Biometrics Division:	IV
Statistical Reviewer:	Dongliang Zhuang, PhD
Concurring Reviewers:	Yan Wang, PhD
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Rhea Lloyd, MD; William Boyd, MD; Wiley Chambers, MD
Project Manager:	Christina Marshall. M.S.

Keywords: diabetic retinopathy (DR) , best corrected visual acuity (BCVA), Early Treatment Diabetic Retinopathy Study (ETDRS)

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The purpose of this supplemental Biologics License Application (sBLA) 125156/S-106 was to support the revision of the Lucentis® U.S. Package Insert (USPI) to include a new indication for the treatment of subjects (b) (4)

This sBLA included the analyses of the retinopathy data from studies FVF4168g and FVF4170g, two double-masked, multicenter, randomized, sham-controlled studies that were originally designed and conducted to support the approval of Lucentis® (ranibizumab) 0.3 mg monthly intravitreal injection for the treatment of diabetic macular edema (DME). The subjects in these studies had clinically significant macular edema with center involvement secondary to diabetes mellitus. Because DR is a precursor to the development of macular edema, all subjects in these two studies had DR. Furthermore, the studies enrolled subjects with a wide range of baseline DR severity levels, including sizeable proportions of both non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) subjects.

According to the submission, the main analysis to support the (b) (4) was the proportion of subjects who experienced a ≥ 3-step improvement from baseline in DR severity scale at Month 24 during the sham-controlled period of the study. Subjects treated with ranibizumab demonstrated improvements in DR severity scale in both studies. At Month 24, the proportion of subjects who experienced a ≥ 3-step improvement in DR severity scale in the 0.3 mg ranibizumab group was 17.1% and 9.4%, versus 2.4% and no subjects in the sham group, in Study FVF4168g and Study FVF4170g, respectively. The majority of the subjects who achieved a 3-step improvement in DR severity scale at Month 24 had moderately severe NPDR, severe NPDR, or mild PDR at baseline; a ≥ 3-step improvement translated into a transition from severe NPDR to less severe NPDR or a reversal from high-risk PDR to mild NPDR.

The beneficial effects of ranibizumab treatment at Month 24 were further observed at multiple timepoints and were supported by the analyses of additional DR endpoints. At Month 24, a ≥ 3-step worsening in DR severity score was experienced by 1.7% and 0.9% of subjects in the 0.3 mg group, versus 5.6% and 4.3% in the sham group, in Study FVF4168g and Study FVF4170g, respectively. A lower proportion of subjects in the 0.3 mg group compared with sham subjects progressed to PDR in both studies at Month 24; 3.2% vs. 11.5% in Study FVF4168g and 1.6% vs. 15.0% in Study FVF4170g.

When the results for subjects initially randomized to ranibizumab were compared with those for subjects who were randomized to sham during the initial treatment periods and crossed over to treatment with ranibizumab at Month 25, early ranibizumab treatment was associated with better DR outcomes.

The protocols defined the proportion of subjects who achieved a ≥ 3-step progression from baseline in the DR severity level at 24 months as a secondary efficacy endpoint. Statistical significance was not demonstrated in the individual studies for the comparison of 0.3 mg ranibizumab group with the sham group with respect to this DR endpoint, likely due to the low

incidence of a ≥ 3-step progression and inadequate number of subjects. However, a favorable trend was observed for ranibizumab treatment in slowing DR progression.

An improvement of ≥ 3-step in the DR severity scale was not a pre-specified endpoint in the study protocols. However, it was considered a valid measurement for the clinical benefit of DR therapy and a similarly defined endpoint (an improvement of ≥2 steps in the DR severity scale) had been used in the clinical studies of another anti-VEGF product. Therefore, the treatment effect observed in the endpoint of an improvement of ≥ 3-step in the DR severity scale was unlikely due to chance, a notion that was further substantiated by the low p-values (<0.01) in the comparison of ranibizumab treatment groups and the sham group with respect to this endpoint.

This reviewer concludes that, the analyses of the data from Studies FVF4168g and FVF4170g demonstrated the benefits of ranibizumab in the treatment of DR in subjects with DME. A description of the study findings in the Lucentis USPI is informative for prescribing physicians. Section 14.4 of the label described the DR clinical studies and study results. We agree including Table 7 but suggest expand it to include the (b) (4) . However, we recommend removal of Figure 7 from the label. (b) (4) Because the clinical relevance of this endpoint is not clear to the statistical reviewer, we defer to the clinical team to determine if it is appropriate to include (b) (4) in the label.

2 INTRODUCTION

1.1 Overview

The applicant is seeking approval for a new indication for the use of ranibizumab in the treatment of [redacted] (b) (4) in the United States on the basis of the analyses of retinopathy data from Studies FVF4168g and FVF4170g. Studies FVF4168g and FVF4170g were primarily designed and conducted to support the approval of Lucentis® (ranibizumab) 0.3 mg monthly intravitreal injection for the treatment of diabetic macular edema (DME). All enrolled subjects in these two studies had DR at baseline. The studies evaluated the improvement or worsening of DR based on the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale as assessed from color fundus photographs (FP) by masked graders at an independent reading center.

In addition to its approval for the treatment of DME on 10 August 2012, ranibizuamb was granted approval for neovascular (wet) age-related macular degeneration (30 June 2006) and macular edema following retinal vein occlusion (22 June 2010).

1.1.1 Class and Indication

Diabetic retinopathy is caused by the damage to the blood vessels of the light-sensitive tissue of retina. It is the most common microvascular complication of diabetes (Type 1 or Type 2) and manifests itself in three forms: 1) non-proliferative diabetic retinopathy, 2) proliferative diabetic retinopathy, and 3) diabetic macular edema. Diabetic retinopathy typically progresses from early NPDR to PDR over years at a rate dependent on the systemic control of the metabolic abnormalities in diabetes. Diabetic macular edema, a complication of DR, can develop at any stage of DR, and it occurs with an increasing frequency as DR progresses.

Diabetic retinopathy has been the leading cause of new cases of vision loss and blindness among working-age adults in most developed countries. The current management strategy for DR consists of intensive glycemic control to slow the progression of disease at the early stage of the disease, panretinal laser photocoagulation (PRP) and vitrectomy in advanced stages of disease. No approved medical therapy that alters the natural progression of disease currently exists.

Ranibizumab is a recombinant, humanized monoclonal IgG1 antibody antigen-binding fragment that selectively binds to and neutralizes the biologic activities of vascular endothelial growth factor-A (VEGF-A), a protein that makes blood vessels grow and leak fluid and blood. By blocking this factor, ranibizumab reduces the growth of the blood vessels and controls the leakage and swelling.

1.1.2 History of Drug Development

Studies FVF4168g and FVF4170g were conducted under BB-IND 8633. The results of these two studies led to the approval of ranibizumab for the treatment of DME. The proportion of

subjects with a ≥ 3-step progression from baseline in the ETDRS diabetic retinopathy severity level at 24 months was evaluated in the studies as a secondary efficacy endpoint. Statistical significance was observed in the pooled data, but not in the individual studies, for the comparison of 0.3 mg ranibizumab group with the sham group with respect to this DR endpoint.

The applicant undertook additional analyses of the retinopathy data from studies FVF4168g and FVF4170g. The main analysis was based on the proportion of subjects who achieved a ≥ 3-step improvement on the DR severity scale at Month 24, which was not a pre-specified endpoint in the study protocols, but was considered acceptable by the clinical team.

A Type-B, pre-sBLA meeting was scheduled for 20 May 2014 to discuss the acceptability of the retinopathy data from Studies FVF4168g and FVF4170g to support a new indication. Prior to the meeting, the Agency provided preliminary responses to the applicant (dated 13 May 2014) in which the Agency agreed that the proposed efficacy and safety data from Studies FVF4168g and FVF4170g appeared adequate to support the filing of a sBLA for the treatment of (b) (4) . Furthermore, the Agency agreed with the proposed Statistical Analysis Plan for the Integrated Summary of Efficacy and the proposed sBLA content and structure. The face-to-face meeting was cancelled after the applicant determined that no further clarification was needed.

1.1.3 Studies Reviewed

This submission included additional analyses of the DR data from the Studies FVF4168g and FVF4170g. These two studies were the subject of the review of supplemental BLA (sBLA) 125156/S-076 and their 24-month data formed the basis for the approval of ranibizumab for the treatment of DME. The studies enrolled subjects who had clinically significant macular edema with center involvement secondary to diabetes mellitus. Because DR was a precursor to the development of macular edema, all subjects enrolled in these two studies had DR.

Studies FVF4168g and FVF4170g had identical design. They were Phase III, double-masked, multicenter, randomized, sham-controlled studies conducted in the United States and Latin America. Eligible subjects were randomized in a 1:1:1 ratio to 0.3 mg ranibizumab, 0.5 mg ranibizumab, and sham. A total of 382 subjects and 377 subjects were enrolled in Study FVF4168g and Study FVF4170g, respectively. Approximately 10% of subjects in Study FVF4168g and less than 3% of subjects in Study FVF4170g were enrolled at study sites in Latin America.

1.2 Data Sources

The sBLA submission can be found at "\\cdsesub1\evsprod\BLA125156\0122".

The analysis datasets for individual studies and the integrated summary of efficacy can be found at the following locations:

\\cdsesub1\evsprod\BLA125156\0122\m5\datasets\fvf4168g-ride\analysis
\\cdsesub1\evsprod\BLA125156\0122\m5\datasets\fvf4170g-rise\analysis
\\cdsesub1\evsprod\BLA125156\0122\m5\datasets\ise\analysis

The submission did not include SAS programs that generated the analysis results.

3 STATISTICAL EVALUATION

1.3 Data and Analysis Quality

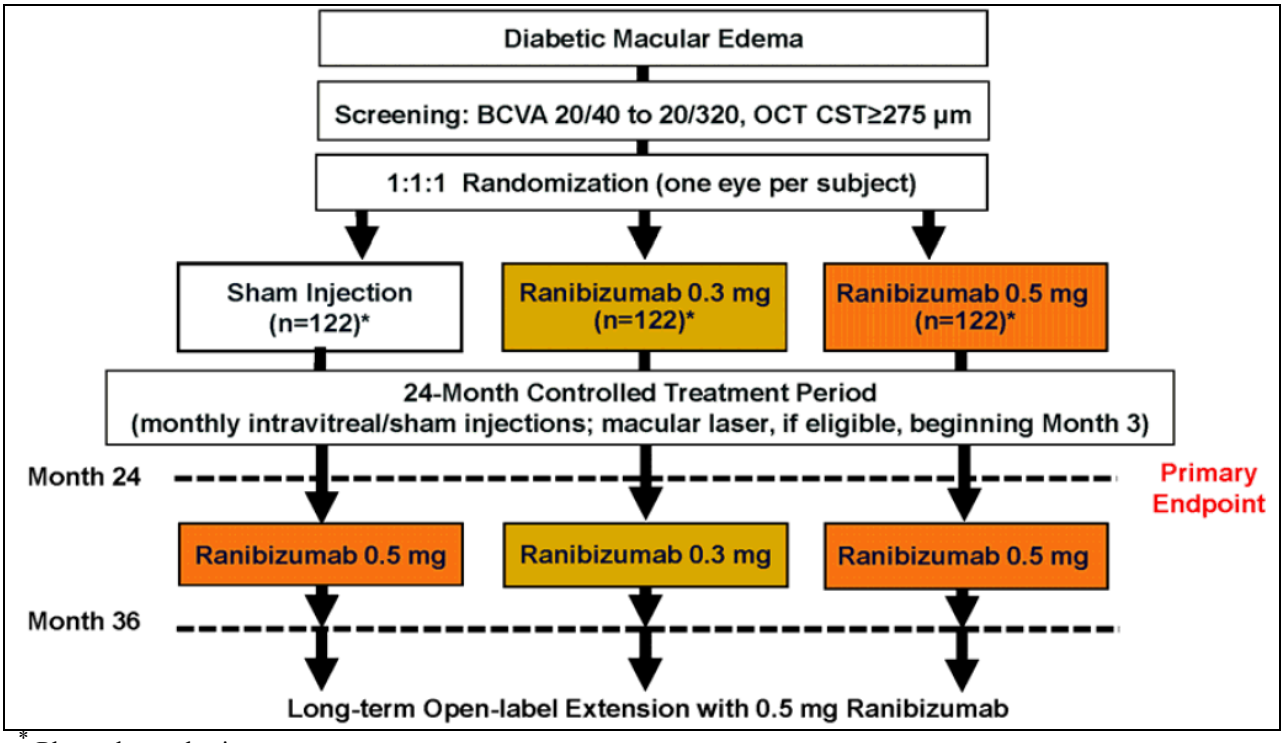
The data didn't conform to SDTM format. However, they adopted the identical structure in terms of the name of the datasets and the name, label, type, format and derivation of the variables throughout the Lucentis development program. The quality of the data and the analyses is acceptable.

1.4 Evaluation of Efficacy

1.4.1 Study Design and Endpoints

Studies FVF4168g and FVF4170g were identical in design; they were Phase III, double masked, multicenter, randomized, sham injection-controlled studies of the efficacy and safety of monthly 0.3 mg or 0.5 mg ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (Type 1 or 2). Schema of the study design is shown in Figure 1.

Figure 1: Schema of the Study Design: FVF4168g and FVF4170g



* Planned sample size.

At the beginning of the 24-month controlled treatment period (Day 0), eligible subjects were randomized in a 1:1:1 ratio to receive 0.5 mg ranibizumab injections, 0.3 mg ranibizumab injections, or sham injections. Randomization was stratified by BCVA in the study eye on Day 0 (≤ 55 letters [approximately 20/80 or worse] vs. > 55 letters [approximately better than 20/80]); baseline glycosylated hemoglobin (HbA1c; ≤ 8% vs. > 8%); prior therapy for diabetic macular edema (DME) in the study eye (yes vs. no); and study site.

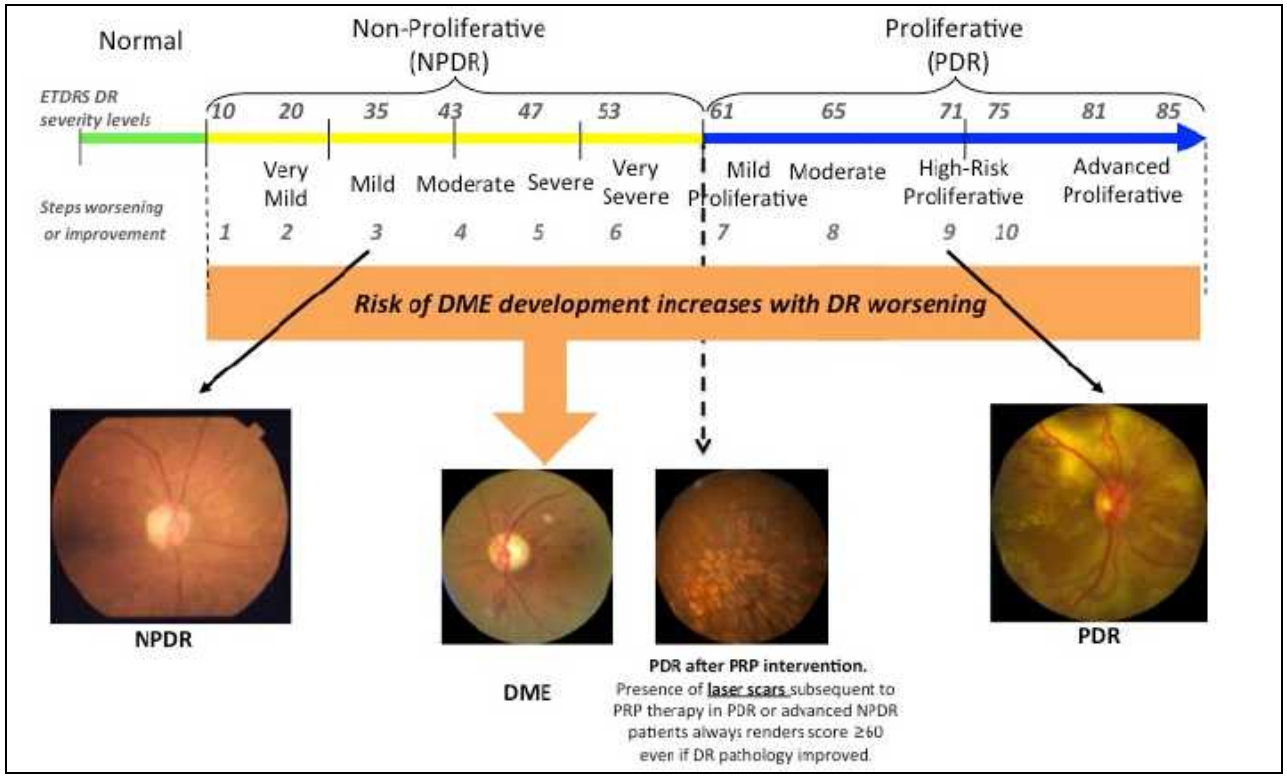
After completing the first 24-month controlled treatment period, subjects randomized to the sham arm were allowed to receive monthly injections of 0.5 mg ranibizumab starting at their Month 25 visit for the remainder of their 36-month masked treatment period (except for a small number of subjects who crossed over from sham early at Month 23 under Protocol Amendment 4).

At the Month 36 visit, subjects who had not prematurely discontinued study treatment could enter the open-label extension phase through Month 60. These subjects received less-frequent-than monthly injection of 0.5 mg ranibizumab (PRN treatment) when their study eyes met retreatment criteria.

These two studies assessed the improvement or worsening of the underlying DR symptoms on an ETDRS DR severity scale based on fundus photographs (FP). Early Treatment Diabetic Retinopathy Study DR severity scale describes the diabetic retinopathy progression in discrete steps (Figure 2). This scale is validated and has been widely used for objective quantification of

retinopathy severity. The disease progression measured on the ETDRS DR severity scale has been shown to be predictive of clinically significant visual function change such as a 15 letters loss in visual acuity, and the incidence of clinically significant macular edema was shown to correlate with the progression of DR from NPDR to PDR. Both 2-step or more and 3-step or more worsening on the ETDRS DR severity scale are associated with an increased risk of subsequent vision loss over time.

Figure 2: Worsening or Improvement of DR Measured on ETDRS DR Severity Scale



Source: Section 2.5: Clinical Overview, Figure 1.

The ETDRS DR severity scale was assessed using fundus photographs (FP) obtained at pre-specified timepoints and evaluated at an independent reading center (University of Wisconsin Fundus Photograph Reading Center) by trained evaluators masked to both treatment assignment and images from previous visits. Each eye was graded by 2 evaluators. In case of disagreement in severity level by more than 1 step, grades were adjudicated by a third senior grader.

Subjects with a history of PRP were assigned to a minimum severity level of 60. These subjects could worsen in DR severity but could not improve to a score less than 60 by definition.

According to the submission, the main analysis to support [redacted] (b) (4) was the proportion of subjects with a ≥ 3-step improvement from baseline in DR severity on the ETDRS DR severity scale at Month 24. This was not a pre-specified endpoint in the study protocols. In the study protocols, the proportion of subjects with a three-step or greater progression from baseline in the ETDRS DR severity level at 24 months was evaluated as a secondary efficacy endpoint. The

studies failed to demonstrate statistical significance in both studies for the comparison between ranibizumab groups and the sham group with respect to this DR endpoint.

The supportive DR efficacy outcome measures included the following:

- Proportion of subjects with a ≥ 3-step improvement from baseline in the ETDRS DR severity score at 36 months, as assessed by the central reading center using FP.
- Proportion of subjects with a ≥ 2-step improvement from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP.
- Proportion of subjects with a ≥ 3-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP.
- Proportion of subjects with a ≥ 2-step worsening from baseline in the ETDRS DR severity score at 24 and 36 months, as assessed by the central reading center using FP.
- Proportion of subjects progressing to PDR as determined by the indirect ophthalmoscopy assessment of the presence of neovascularization on the optic disc, elsewhere on the retina, or iris by Month 24 and 36.
- Time to first new PDR event, where a new PDR event was defined by (1) progression from NPDR (DR severity score < 60) at baseline to PDR (DR severity score ≥ 60) at a later timepoint, (2) use of PRP laser treatment, (3) vitreous hemorrhage (AE or slitlamp grade 0 at baseline to > 0 at a later timepoint), (4) cases identified by ophthalmoscopy as described above, (5) use of vitrectomy for reasons related to DR or its complications, (6) iris neovascularization AE, or (7) retinal neovascularization AE, whichever occurred first. Subjects with a baseline DR severity score ≥ 60 were considered as having experienced a new PDR event if any one of the conditions as described in (2) to (7) occurred.

Based on my discussion with the Medical Reviewer, the composite endpoint that defined the time to first new PDR event is not a clinically relevant endpoint.

1.4.2 Statistical Methodologies

The efficacy analyses were performed using data from the intent-to-treat (ITT) population unless otherwise noted. The ITT population was defined to include all subjects who were randomized to treatment, regardless of whether or not they actually received treatment.

All efficacy analyses were for the study eye. Subjects whose baseline DR severity was not graded were excluded in the assessment of DR progression and improvement from baseline. Missing DR data, including those reported as non-gradable, during the 36-month masked treatment period were imputed using the last-observation-carried-forward (LOCF) imputation method. Sensitivity analyses based on observed data were also performed.

Data from Studies FVF4168g and FVF4170g were analyzed for each study individually and for both studies combined. Subgroup analyses were performed for the main efficacy endpoint based on the pooled data from Studies FVF4168g and FVF4170g.

For the analysis of the proportion of subjects with a 3-step or greater improvement from baseline in the ETDRS diabetic retinopathy severity level at 24 months, each ranibizumab group was

compared to the control group using the Cochran-Mantel-Haenszel chi-square test, with adjustment for stratification factors: baseline visual acuity (≤ 55 letters, > 55 letters), baseline HbA1c (≤ 8%, > 8%), and prior treatment for diabetic macular edema (yes, no). Other proportion endpoints were analyzed similarly.

1.4.3 Subject Disposition, Demographic and Baseline Characteristics

Because the baseline and demographic data from Studies FVF4168g and FVF4170g had been summarized extensively in the review of sBLA 125156/S-076, we present here only the subject disposition, demographic and baseline characteristics that are relevant to the evaluation of DR endpoints.

More than 80% of the randomized subjects completed the follow-up through Month 24 in both studies. The proportion of subjects who completed the follow-up through Month 36 was close to 80% with the exception of the sham group in Study FVF4170g, in which only 67.7% of subjects completed the follow-up through Month 36.

Table 1: Subject Disposition

Category	Study FVF 4168g			Study FVF 4170g		
		Ranibizumab			Ranibizumab	
	Sham (n=130)	0.3 mg (n=125)	0.5 mg (n=127)	Sham (n=127)	0.3 mg (n=125)	0.5 mg (n=125)
Intent-to-Treat	130 (100%)	125 (100%)	127 (100%)	127 (100%)	125 (100%)	125 (100%)
Completed study through Month 24	108 (83.1%)	105 (84.0%)	110 (86.6%)	102 (80.3%)	105 (84.0%)	106 (84.8%)
Discontinued study prior to Month 24	22 (16.9%)	20 (16.0%)	17 (13.4%)	25 (19.7%)	20 (16.0%)	19 (15.2%)
Completed study through Month 36	102 (78.5%)	98 (78.4%)	98 (77.2%)	86 (67.7%)	98 (78.4%)	100 (80.0%)
Discontinued study prior to Month 36	28 (21.5%)	27 (21.6%)	29 (22.8%)	41 (32.3%)	27 (21.6%)	25 (20.0%)

Note: Completion/discontinuation status was based on the entry in 'Early study discontinuation reason (M24)' and 'Early study discontinuation reason (M36)' in dataset TXSTUDY. Subject count is different when 'Completed follow-up through M24 (yes/No)' or 'Completed follow-up through M36 (yes/No)' is used. For example, subject 51003 (FVF4168g, 0.3 mg) was indicated to be a 24-month completer (the subject had visits beyond Month 24 even though she did not attend Month 24 visit). However, a discontinuation reason was entered for this subject. This subject and two other subjects (57102, FVF4168g, 0.5 mg; 76403, FVF4170g, 0.5 mg) did not have a discontinuation reason, but they were indicated to be 36-month non-completers.

Source: Integrated Summary of Efficacy (ISE), Table 4.

The number of subjects who had ETDRS DR severity evaluation at each visit is presented in Table 2. The majority of subjects completed DR severity assessment through Month 36.

Table 2: Number of Subjects with ETDRS DR Severity Evaluation at Each Visit

				FVF4168G				
Treatment	Baseline	M3	M6	M12	M18	M24	M30	M36
Sham	128	111	108	105	99	102	99	99
0.3 mg RBZ	124	112	104	108	98	97	89	97
0.5 mg RBZ	126	119	112	108	103	102	101	91
				FVF4170G				
Sham	126	114	102	100	96	95	86	84
0.3 mg RBZ	121	115	108	98	98	100	91	96
0.5 mg RBZ	121	114	103	107	98	102	87	94

Source: Reviewer's analysis.

The ETDRS DR severity scale at baseline is presented in Table 3. The study population in Studies FVF4168g and FVF4170g had a broad spectrum of DR severity levels at baseline, including mild, moderate, and severe NPDR as well as PDR. Approximately 22% to 32% of subjects had moderately severe NPDR, and 25% to 30% of subjects had mild PDR at baseline

(including subjects who were assigned a minimum ETDRS level-60 retinopathy due to the scars from previous PRP).

Table 3: Baseline ETDRS DR Severity Level (Randomized Subjects with DR Severity Evaluation at Baseline)

	Study FVF 4168g			Study FVF 4170g		
		Ranibizumab			Ranibizumab	
Category	Sham (n=128)	0.3 mg (n=124)	0.5 mg (n=126)	Sham (n=126)	0.3 mg (n=121)	0.5 mg (n=121)
10, 12 (DR absent)	1 (0.8%)	0	1 (0.8%)	0	1 (0.8%)	0
14A-14C, 14Z, 15, 20 (DR questionable, microaneurysms only)	3 (2.3%)	1 (0.8%)	1 (0.8%)	0	2 (1.7%)	2 (1.7%)
35A-35F (mild NPDR)	21 (16.4%)	20 (16.1%)	17 (13.5%)	17 (13.5%)	19 (15.7%)	25 (20.7%)
43A, 43B (moderate NPDR)	12 (9.4%)	13 (10.5%)	18 (14.3%)	21 (16.7%)	16 (13.2%)	16 (13.2%)
47A-47D (moderately severe NPDR)	38 (29.7%)	35 (28.2%)	28 (22.2%)	34 (27.0%)	39 (32.2%)	36 (29.8%)
53A-53E (severe NPDR)	6 (4.7%)	9 (7.3%)	6 (4.8%)	8 (6.3%)	5 (4.1%)	4 (3.3%)
60, 61A, 61B (mild PDR)	32 (25.0%)	32(25.8%)	38 (30.2%)	32 (25.4%)	32 (26.4%)	31 (25.6%)
65A-65C (moderate PDR)	9 (7.0%)	5 (4.0%)	8 (6.3%)	3 (2.4%)	2 (1.7%)	1 (0.8%)
71A-71D (high-risk PDR)	2 (1.6%)	2 (1.6%)	1 (0.8%)	0	1 (0.8%)	0
75 (high-risk PDR)	0	0	1 (0.8%)	0	0	0
90 (cannot grade)	4 (3.1%)	7 (5.6%)	7 (5.6%)	11 (8.7%)	4 (3.3%)	6 (5.0%)

Note: DR = diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

Source: Integrated Summary of Efficacy, Table 8.

The ETDRS DR severity scale at baseline is further categorized into several groups in Table 4. An ETDRS severity level ≤ 35 corresponds to a disease status less severe than mild NPDR; an ETDRS severity level ≥ 60 corresponds to a PDR or more advanced DR disease status.

Table 4: Categorization of Baseline ETDRS DR Severity Level (Randomized Subjects with DR Severity Evaluation at Baseline)

	Study FVF 4168g			Study FVF 4170g		
		Ranibizumab			Ranibizumab	
Category; n (%)	Sham (n=128)	0.3 mg (n=124)	0.5 mg (n=126)	Sham (n=126)	0.3 mg (n=121)	0.5 mg (n=121)
≤ 35	25 (19.5%)	21 (16.9%)	19 (15.1%)	17 (13.5%0	22 (18.2%)	27 (22.3%)
> 35	99 (77.3%)	96 (77.4%)	100 (79.4%)	98 (77.8%)	95 (78.5%)	88 (72.7%)
< 60	81 (63.3%)	78 (62.9%)	71 (56.3%)	80 (63.5%)	82 (67.8%)	83 (68.6%)
≥ 60	43 (33.6%)	39 (31.5%)	48 (38.1%)	35 (27.8%)	35 (28.9%)	32 (26.4%)
90 (cannot grade)	4 (3.1%)	7 (5.6%)	7 (5.6%)	11 (8.7%)	4 (3.3%)	6 (5.0%)

Source: Reviewer's analysis.

Table 5 presents the diabetic retinopathy history of the study eye for randomized subjects. Active or previously treated PDR was present in more than 20% of the randomized subjects in each treatment group. The percentage of subjects who had received PRP laser varied, ranging from 15% to 23%. Approximately 90% of the subjects had a history of NPDR and the mean time from first known NPDR diagnosis to randomization ranged from 2.2 years to 3.0 years.

Table 5: Diabetic Retinopathy History in Study Eye (Randomized Subjects)

	Study FVF 4168g			Study FVF 4170g		
		Ranibizumab			Ranibizumab	
Category	Sham (n=130)	0.3 mg (n=125)	0.5 mg (n=127)	Sham (n=127)	0.3 mg (n=125)	0.5 mg (n=125)
Active or previously treated PDR present	28 (21.5%)	31 (24.8%)	34 (26.8%)	34 (26.8%)	28 (22.4%)	32 (25.6%)
Received panretinal photocoagulation (PRP)	20 (15.4%)	29 (23.2%)	29 (22.8%)	31 (24.4%)	24 (19.2%)	27 (21.6%)
NPDR present	117 (90.0%)	116 (92.8%)	112 (88.2%)	112 (88.2%)	111 (88.8%)	114 (91.2%)
Time from 1st known NPDR diagnosis to randomization (yr); n, mean (SD)	117 3.0 (3.6)	114 2.5 (4.3)	112 2.5 (3.1)	112 2.3 (2.5)	109 2.2 (2.3)	113 2.5 (3.1)

Source: Integrated Summary of Efficacy, Table 10.

The demographic and baseline characteristics are presented in Table 6. The three treatment groups were generally balanced in terms of demographics and baseline characteristics, including baseline ocular and anatomical characteristics of the study eye.

Table 6: Demographic and Baseline Characteristics (Randomized Subjects)

	Study FVF 4168g			Study FVF 4170g		
		Ranibizumab			Ranibizumab	
Category	**Sham (n=130)**	**0.3 mg (n=125)**	**0.5 mg (n=127)**	**Sham (n=127)**	**0.3 mg (n=125)**	**0.5 mg (n=125)**
Age (year); Mean (SD)	63.5 (10.8)	62.7 (11.1)	61.8 (10.1)	61.8 (9.8)	61.7 (8.9)	62.8 (10.0)
Age Group; n (%)						
< 65 years	69 (53.1%)	70 (56.0%)	72 (56.7%)	79 (62.2%)	78 (62.4%)	62 (49.6%)
≥ 65 years	61 (46.9%)	55 (44.0%)	55 (43.3%)	48 (37.8%)	47 (37.6%)	63 (50.4%)
Sex; n (%)						
Male	66 (50.8%)	73 (58.4%)	80 (63.0%)	74 (58.3%)	73 (58.4%)	65 (52.0%)
Female	64 (49.2%)	52 (41.6%)	47 (37.0%)	53 (41.7%)	52 (41.6%)	60 (48.0%)
Race; n (%)						
White	104 (80.0%)	99 (79.2%)	105 (82.7%)	101 (79.5%)	97 (77.6%)	97 (77.6%)
Black or African American	15 (11.5%)	14 (11.2%)	13 (10.2%)	19 (15.0%)	18 (14.4%)	14 (11.2%)
Other	11 (8.5%)	12 (9.6%)	9 (7.1%)	7 (5.5%)	10 (8.0%)	14 (11.2%)
HbA1c						
n	126	120	124	124	120	120
Mean (SD)	7.6 (1.4)	7.6 (1.3)	7.6 (1.4)	7.7 (1.5)	7.7 (1.5)	7.7 (1.4)
HbA1c Group; n (%)						
n	126	120	124	124	120	120
≤ 8	85 (67.5%)	79 (65.8%)	84 (67.7%)	80 (64.5%)	81 (67.5%)	82 (68.3%)
> 8	41 (32.5%)	41 (34.2%)	40 (32.3%)	44 (35.5%)	39 (32.5%)	38 (31.7%)
Prior Therapy for DME; n (%)						
Yes	92 (70.8%)	85 (68.0%)	88 (69.3%)	94 (74.0%)	94 (75.2%)	102 (81.6%)
No	38 (29.2%)	40 (32.0%)	39 (30.7%)	33 (26.0%)	31 (24.8%)	23 (18.4%)
BCVA Score; Mean (SD)	57.3 (11.2)	57.5 (11.6)	56.9 (11.8)	57.2 (11.1)	54.7 (12.6)	56.9 (11.6)
BCVA Group; n (%)						
≤ 55 letters	50 (38.5%)	50 (40.0%)	46 (36.2%)	51 (40.2%)	59 (47.2%)	48 (38.4%)
> 55 letters	80 (61.5%)	75 (60.0%)	81 (63.8%)	76 (59.8%)	66 (52.8%)	77 (61.6%)

Source: Integrated Summary of Efficacy, Tables 7 & 9.

1.4.4 Results and Conclusions

1.4.4.1 DR Severity Improvement or Progression

The main analysis in this submission was the proportion of subjects who experienced a ≥ 3-step improvement from baseline in DR severity on the ETDRS DR severity scale at Month 24 during the sham-controlled period. The analysis was supported by the analyses of the other DR outcomes including the proportion of subjects who experienced a ≥ 2-step improvement from baseline in DR severity on the ETDRS DR severity scale at Month 24, the proportion of subjects who experienced a ≥ 3-step worsening from baseline in DR severity on the ETDRS DR severity scale at Month 24, and the proportion of subjects who experienced a ≥ 2-step worsening from baseline in DR severity on the ETDRS DR severity scale at Month 24. The analysis results for these endpoints are presented in Table 7 for two studies.

Table 7: Diabetic Retinopathy Efficacy Data at Month 24 (Randomized Subjects with a Gradable Baseline DR Severity Score; LOCF Method)

	Treatment		
	Sham	**0.3 mg Ranibizumab**	**0.5 mg Ranibizumab**
Study FVF4168g			
N	124	117	119
Improved ≥ 3 steps	3 (2.4%)	20 (17.1%)	21 (17.6%)
Difference (95% CI) [a]		14.5% (7.4%, 21.7%)	15.0% (7.8%, 22.2%)
p-value [b]		0.0002	0.0001
Improved ≥ 2 steps	5 (4.0%)	45 (38.5%)	43 (36.1%)
Difference (95% CI) [a]		34.8% (25.5%, 44.1%)	32.0% (22.8%, 41.2%)
p-value [b]		<0.0001	<0.0001
Progressed ≥ 3 steps	7 (5.6%)	2 (1.7%)	0
Difference (95% CI) [a]		-4.2% (-9.3%, 0.8%)	-5.8% (-9.8%, -1.7%)
p-value [b]		0.0853	0.0073
Progressed ≥ 2 steps	13 (10.5%)	2 (1.7%)	0
Difference (95% CI) [a]		-8.5% (-14.4%, -2.6%)	-10.6% (-16.0%, -5.3%)
p-value [b]		0.0075	0.0003
Study FVF4170g			
N	115	117	115
Improved ≥ 3 steps	0	11 (9.4%)	13 (11.3%)
Difference (95% CI) [a]		8.9% (4.0%, 13.7%)	11.7% (5.9%, 17.4%)
p-value [b]		0.0014	0.0001
Improved ≥ 2 steps	8 (7.0%)	43 (36.8%)	41 (35.7%)
Difference (95% CI) [a]		30.5% (20.9%, 40.2%)	28.3% (18.9%, 37.7%)
p-value [b]		<0.0001	<0.0001
Progressed ≥ 3 steps	5 (4.3%)	1 (0.9%)	2 (1.7%)

Difference (95% CI) [a]		-3.0% (-6.7%, 0.7%)	-2.5% (-6.5%, 1.4%)
p-value [b]		0.1590	0.2721
Progressed ≥ 2 steps	10 (8.7%)	1 (0.9%)	5 (4.3%)
Difference (95% CI) [a]		-7.7% (-13.0%, -2.4%)	-4.5% (-10.6%, 1.6%)
p-value [b]		0.0069	0.1765
Pooled			
N	239	234	234
Improved ≥ 3 steps	3 (1.3%)	31 (13.2%)	14 (14.5%)
Difference (95% CI) [a]		11.7% (7.3%, 16.1%)	13.3% (8.6%, 18.0%)
p-value [b]		<0.0001	<0.0001
Improved ≥ 2 steps	13 (5.4%)	88 (37.6%)	84 (35.9%)
Difference (95% CI) [a]		32.6% (25.9%, 39.4%)	30.4% (23.7%, 37.1%)
p-value [b]		<0.0001	<0.0001
Progressed ≥ 3 steps	12 (5.0%)	3 (1.3%)	2 (0.9%)
Difference (95% CI) [a]		-3.5% (-6.6%, -0.3%)	-4.2% (-7.2%, -1.2%)
p-value [b]		0.0355	0.0072
Progressed ≥ 2 steps	23 (9.6%)	3 (1.3%)	5 (2.1%)
Difference (95% CI) [a]		-8.1% (-12.1%, -4.1%)	-7.6% (-11.7%, -3.4%)
p-value [b]		0.0001	0.0005

Note: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA1c (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

[b] From Cochran-Mantel-Haenszel chi-square tests adjusted for the baseline strata.

Source: Integrated Summary of Efficacy, Table 2.

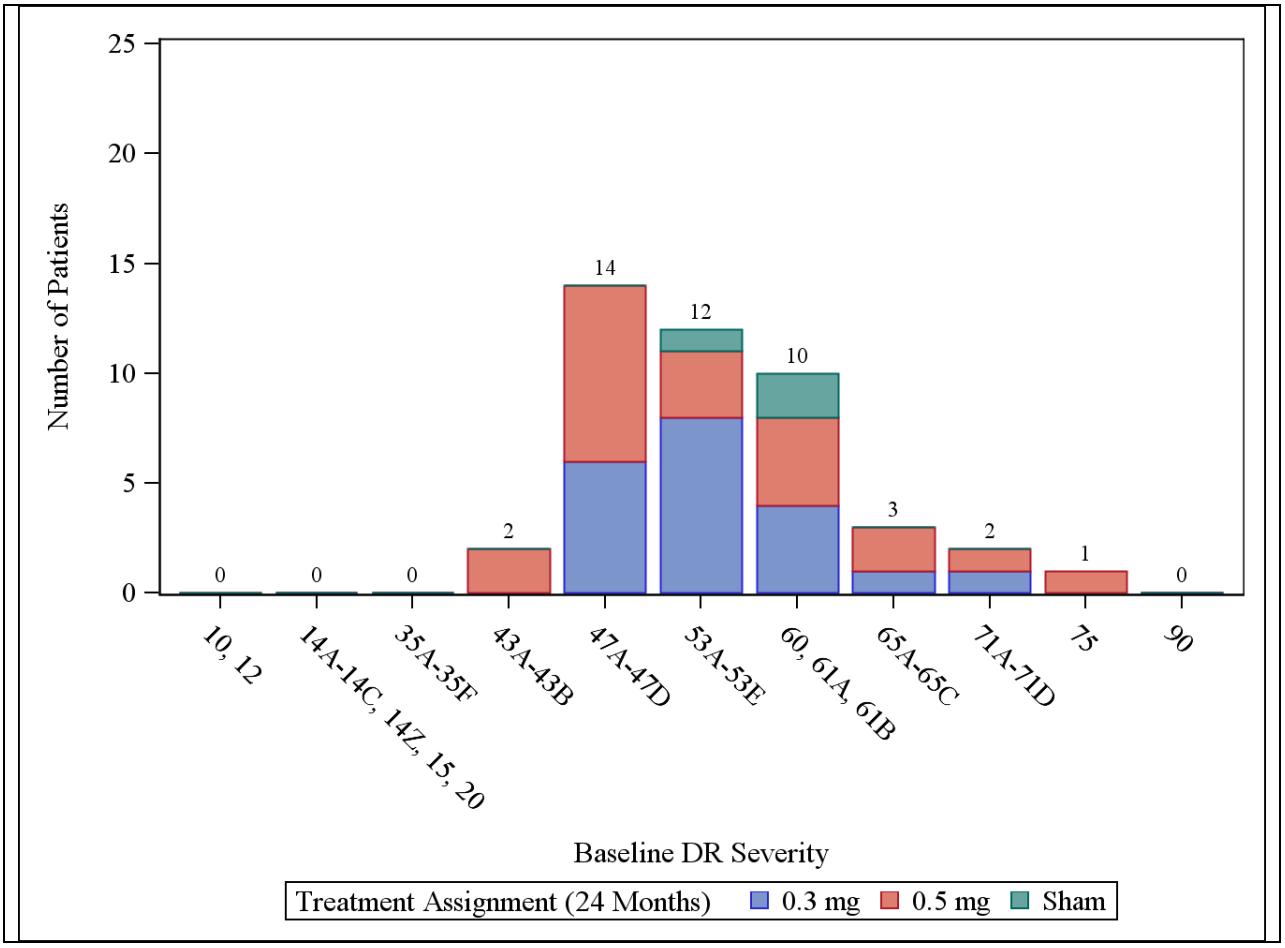
A significantly higher proportion of ranibizumab-treated subjects compared with control subjects achieved ≥ 3 steps improvement in DR severity scale in both studies at Month 24. In Study FVF4168g, 17.1% and 17.6% of subjects in the 0.3 mg and 0.5 mg ranibizumab groups experienced ≥ 3-step improvement in ETDRS DR severity scale vs. 2.4% in the sham group ($p = 0.0002$ and $p = 0.0001$ for the 0.3 mg and 0.5 mg group vs. sham, respectively) at Month 24. In Study FVF4170g, 9.4% and 11.3% of subjects in the 0.3 mg and 0.5 mg ranibizumab groups experienced ≥ 3-step improvement in ETDRS DR severity scale vs. no subjects in the sham group ($p = 0.0014$ and 0.0001 for 0.3 mg and 0.5 mg group vs. sham, respectively) at Month 24. The analysis of the proportion of subjects with a ≥ 3-step improvement in ETDRS-DR severity scale at Month 24 using the observed data yielded similar results.

A greater difference between ranibizumab groups and control group was observed in the proportion of subjects who experienced a ≥ 2-step improvement from baseline in DR severity on the ETDRS DR severity scale at Month 24.

Only few subjects experienced a ≥ 3-step or ≥ 2-step worsening from baseline in DR severity on the ETDRS DR severity scale at Month 24. This was especially true for ranibizumab-treated subjects. The treatment comparison between the ranibizumab groups and the sham was not statistically significant with respect to these two endpoints.

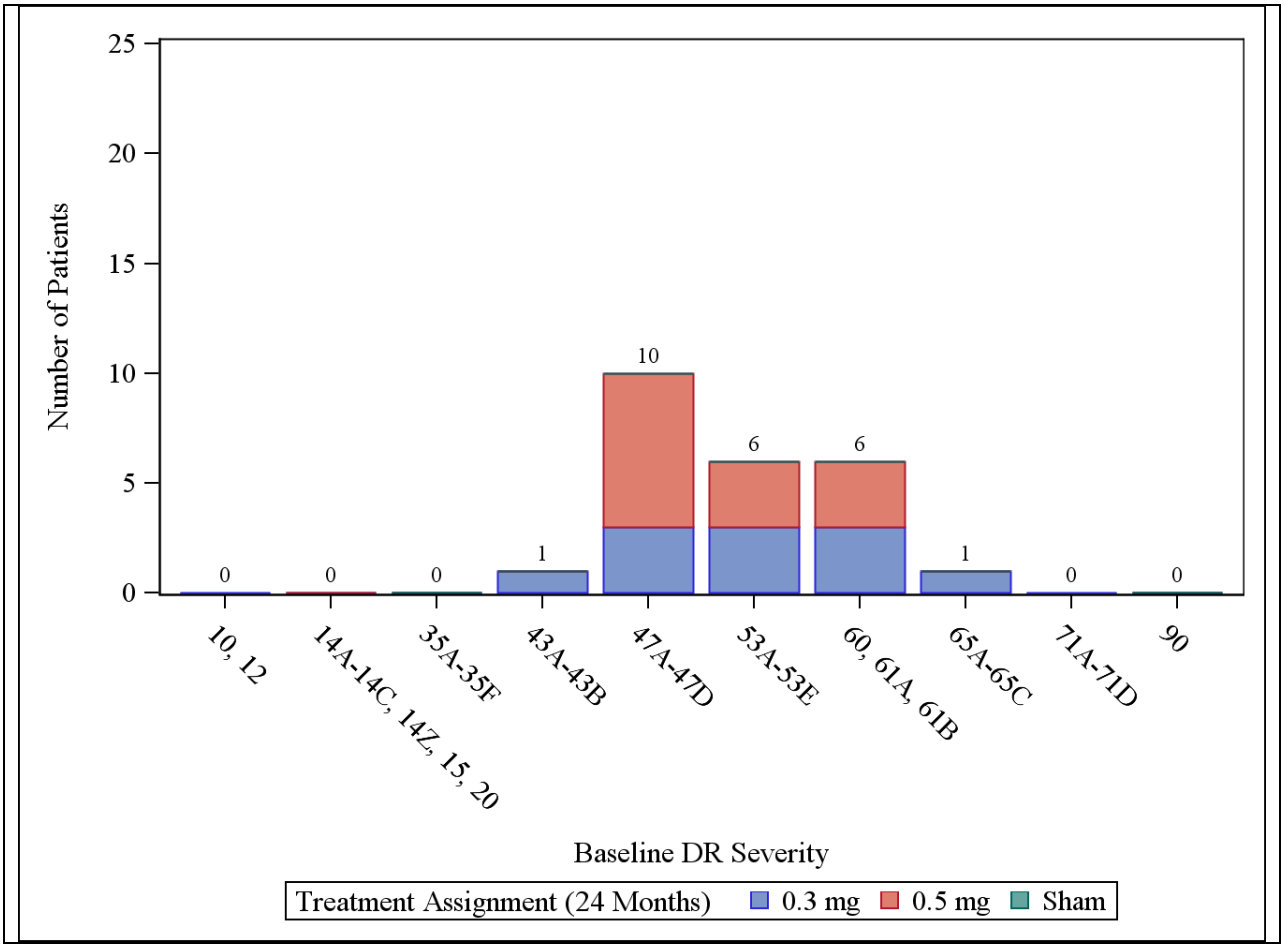
Figure 3 and Figure 4 display the number of subjects who achieved 3-step improvement in DR severity scale at Month 24 by the baseline DR severity. The majority of the subjects who achieved 3-step improvement in DR severity scale at Month 24 had moderately severe NPDR, severe NPDR, or mild PDR at baseline. Therefore, a ≥ 3-step improvement could translate into a transition from severe NPDR to less severe NPDR or a reversal from high-risk PDR to mild NPDR.

Figure 3: Number of Subjects Who Achieved ≥ 3 Steps Improvement in DR Severity Scale at Month 24 (Randomized Subjects with a Gradable Baseline DR Severity Score in Study FVF4168g; LOCF Method)



Source: Reviewer's analysis.

Figure 4: Number of Subjects Who Achieved ≥ 3 steps Improvement in DR Severity Scale at Month 24 (Randomized Subjects with a Gradable Baseline DR Severity Score in Study FVF4170g; LOCF Method)



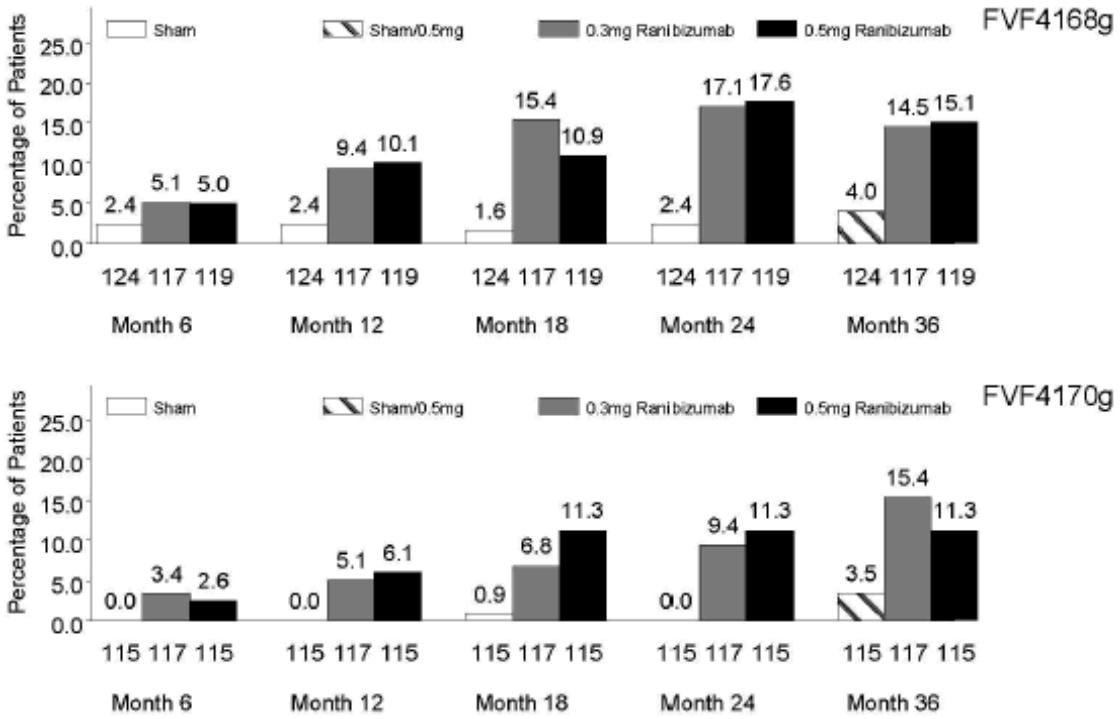
Source: Reviewer's analysis.

The ≥ 3-step improvements from baseline in the ETDRS DR severity score achieved for subjects in the ranibizumab groups were observed at earlier timepoints and the treatment effect at Month 24 were maintained at Month 36 (Figure 5). In Study FVf4168g, 14.5% and 15.1% of subjects in the 0.3 mg and 0.5 mg groups had ≥ 3-step improvement in ETDRS DR severity score vs. 4.0% in the sham/0.5-mg group ($p = 0.0107$ and $p = 0.0042$ for the 0.3-mg and 0.5-mg group vs. sham/0.5 mg respectively) at Month 36. In Study FVF4170g, 15.4% and 11.3% of subjects in the 0.3 mg and 0.5 mg groups had a ≥ 3-step improvement in ETDRS DR severity score vs. 3.5% in the sham/0.5-mg group ($p = 0.0031$ and $p = 0.0170$ for 0.3-mg and 0.5-mg group vs. sham/0.5 mg, respectively) at Month 36 (Table 8).

Most subjects who were randomized to sham during the initial 24-month treatment period crossed over to receive ranibizumab 0.5 mg at Month 25 and continued monthly treatment through Month 36. However, these subjects did not achieve the same DR benefit as those

originally randomized to ranibizumab treatment. Therefore, delayed ranibizumab treatment may negatively affect the magnitude of response that can be otherwise obtained.

Figure 5: Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye Over Time (Studies FVF4168g and FVF4170g; Randomized Subjects with a Gradable Score at Baseline; LOCF Method)



Source: Integrated Summary of Efficacy, Figure 9.

Table 8: Diabetic Retinopathy Efficacy Data at Month 36 (Randomized Subjects with a Gradable Baseline DR Score; LOCF Method)

	Treatment		
	Sham/0.5 mg Ranibizumab	**0.3 mg Ranibizumab**	**0.5 mg Ranibizumab**
Study FVF4168g			
N	124	117	119
Improved ≥ 3 steps	5 (4.0%)	17 (14.5%)	18 (15.1%)
Difference (95% CI) [a]		9.7% (2.7%, 16.7%)	10.8% (3.8%, 17.8%)
p-value [b]		0.0107	0.0042
Study FVF4170g			
N	115	117	115
Improved ≥ 3 steps	4 (3.5%)	18 (15.4%)	13 (11.3%)
Difference (95% CI) [a]		11.4% (4.5%, 18.3%)	8.4% (2.2%, 14.6%)
p-value [b]		0.0031	0.0170

Note: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA1c (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

[b] From Cochran-Mantel-Haenszel chi-square tests adjusted for the baseline strata.

Source: Integrated Summary of Efficacy, Table 13.

The distribution of DR severity scale at Month 24 and Month 36 is displayed in Table 9 and Table 10 for Studies FVF4168g and FVF4170g, respectively. Compared to the distribution at baseline, more subjects were observed to have mild NPDR as a result of improvement in DR severity for the ranibizumab-treated subjects.

Table 9: ETDRS DR Severity Level at Month 24 (Randomized Subjects with a Gradable DR Severity Score; LOCF)

	Study FVF 4168g			Study FVF 4170g		
		Ranibizumab			Ranibizumab	
Category	Sham (n=128)	0.3 mg (n=125)	0.5 mg (n=125)	Sham (n=124)	0.3 mg (n=122)	0.5 mg (n=123)
10, 12 (DR absent)	1 (0.8%)	2 (1.6%)	9 (7.2%)	0	2 (1.6%)	5 (4.1%)
14A-14C, 14Z, 15, 20 (DR questionable, microaneurysms only)	3 (2.3%)	16 (12.8%)	15 (12.0%)	1 (0.8)	13 (10.7%)	20 (16.3%)
35A-35F (mild NPDR)	28 (21.9%)	53 (42.4%)	49 (39.2%)	35 (28.2%)	60 (49.2%)	53 (43.1%)
43A, 43B (moderate NPDR)	25 (19.5%)	8 (6.4%)	4 (3.2%)	17 (13.7%)	10 (8.2%)	7 (5.7%)
47A-47D (moderately severe NPDR)	17 (13.3%)	6 (4.8%)	4 (3.2%)	18 (14.5%)	4 (3.3%)	3 (2.4%)
53A-53E (severe NPDR)	4 (3.1%)	0	1 (0.8%)	2 (1.6%)	0	0
60, 61A, 61B (mild PDR)	36 (28.1%)	40 (32.0%)	41 (32.8%)	46 (37.1%)	31 (25.4%)	34 (27.6%)
65A-65C (moderate PDR)	7 (5.5%)	0	2 (1.6%)	4 (3.2%)	2 (1.6%)	0
71A-71D (high-risk PDR)	4 (3.1%)	0	0	1 (0.8%)	0	1 (0.8%)
75 (high-risk PDR)	1 (0.8%)	0	0	0	0	0
85A, 85B ((high-risk PDR)	2 (1.6%)	0	0	0	0	0

Note: DR = diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.
Source: Reviewer's analysis.

Table 10: ETDRS DR Severity Level at Month 36 (Randomized Subjects with a Gradable DR Severity Score; LOCF)

	Study FVF 4168g			Study FVF 4170g		
		Ranibizumab			Ranibizumab	
Category	Sham/ 0.5 mg (n=128)	0.3 mg (n=125)	0.5 mg (n=125)	Sham/ 0.5 mg (n=124)	0.3 mg (n=122)	0.5 mg (n=123)
10, 12 (DR absent)	4 (3.1%)	6 (4.8%)	12 (9.6%)	2 (1.6%)	6 (4.9%)	12 (9.8%)
14A-14C, 14Z, 15, 20 (DR questionable, microaneurysms only)	5 (3.9%)	8 (6.4%)	10 (8.0%)	9 (7.3%)	19 (15.6%)	13 (10.6%)
35A-35F (mild NPDR)	48 (37.5%)	57 (45.6%)	47 (37.6%)	44 (35.5%)	50 (41.0%)	55 (44.7%)
43A, 43B (moderate NPDR)	14 (10.9%)	7 (5.6%)	7 (5.6%)	10 (8.1%)	7 (5.7%)	6 (4.9%)
47A-47D (moderately severe NPDR)	5 (3.9%)	7 (5.6%)	3 (2.4%)	7 (5.6%)	4 (3.3%)	4 (3.3%)
53A-53E (severe NPDR)	2 (1.6%)	0	1 (0.8%)	1 (0.8%)	0	0
60, 61A, 61B (mild PDR)	46 (35.9%)	39 (31.2%)	44 (35.2%)	49 (39.5%)	33 (27.0%)	32 (26.0%)
65A-65C (moderate PDR)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	2 (1.6%)	0
71A-71D (high-risk PDR)	2 (1.6%)	0	0	1 (0.8%)	1 (0.8%)	1 (0.8%)
75 (high-risk PDR)	0	0	0	0	0	0
85A, 85B ((high-risk PDR)	1 (0.8%)	0	0	0	0	0

Note: DR = diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.
Source: Reviewer's analysis.

In Table 11 and Table 12, the DR efficacy data at the last visit during the 24-month follow-up period is summarized according to the 24-month completion status. These summaries included subjects who had a DR severity assessment at baseline (including the subjects whose DR severity scale at baseline could not be graded). The purpose of this analysis is to examine whether the improvement/progression in DR severity was similar between the subjects who completed the 24-month follow-up and the subjects who discontinued from the study prior to Month 24 visit.

In both studies, subjects who discontinued from the study prior to Month 24 tended to be less likely to experience improvement in DR severity compared to the subjects who completed the 24-month follow-up. However, the number of subjects who discontinued from the study prior to Month 24 was small and the number of subjects who had DR severity assessment prior to the discontinuation was even smaller, which makes a comparison of the subjects who completed the 24-month follow-up with the subjects who discontinued from the study prior to Month 24 with respect to the DR severity scale change difficult.

Table 11: Diabetic Retinopathy Efficacy Data at Last Visit during 24-Month Follow-up Period by 24-Month Completion Status (Randomized Subjects in Study FVF4168g)

	Study FVF4168g		
	Sham	**0.3 mg Ranibizumab**	**0.5 mg Ranibizumab**
Having Baseline DR Severity Scale	128	124	126
Completed Follow-up through Month 24	108	105	109
DR Severity Scale Change; n (%) [1]			
Improved ≥ 3 steps	2 (1.9%)	19 (18.1%)	21 (19.3%)
Improved ≥ 2 steps	4 (3.7%)	42 (40.0%)	40 (36.7%)
Progressed ≥ 3 steps	5 (4.6%)	2 (1.9%)	0 (%)
Progressed ≥ 2 steps	9 (8.3%)	2 (1.9%)	0 (%)
Missing	8 (7.4%)	8 (7.6%)	10 (9.2%)
No Post-baseline	0	0	0
Cannot grade at baseline only	2	5	5
Cannot grade at last visit only	5	3	5
Cannot grade at baseline and last visit	1	0	0
Discontinued prior to Month 24	20	19	17
DR Severity Scale Change; n (%) [2]			
Improved ≥ 3 steps	1 (5.0%)	0 (0%)	0 (0%)
Improved ≥ 2 steps	1 (5.0%)	2 (10.5%)	3 (17.6%)
Progressed ≥ 3 steps	1 (5.0%)	0 (0%)	0 (0%)
Progressed ≥ 2 steps	3 (15.0%)	0 (0%)	0 (0%)
Missing	6 (30.0%)	6 (31.6%)	6 (35.3%)
No Post-baseline	5	4	4
Cannot grade at baseline only	1	2	0
Cannot grade at last visit only	0	0	0
Cannot grade at baseline and last visit	0	0	2

[1] The denominator is the number of subjects who completed follow-up through Month 24.
[2] The denominator is the number of subjects who discontinued prior to Month 24.
Source: Reviewer's analysis.

Table 12: Diabetic Retinopathy Efficacy Data at Last Visit during 24-Month Follow-up Period by 24-Month Completion Status (Randomized Subjects in Study FVF4170g)

	Study FVF4170g		
	Sham	**0.3 mg Ranibizumab**	**0.5 mg Ranibizumab**
Having Baseline DR Severity Scale	126	121	121
Completed Follow-up through Month 24	101	103	103
DR Severity Scale Change; n (%) [1]			
Improved ≥ 3 steps	0 (0%)	11 (10.7%)	12 (11.7%)
Improved ≥ 2 steps	7 (6.9%)	38 (36.9%)	35 (34.0%)
Progressed ≥ 3 steps	5 (5.0%)	1 (1.0%)	2 (1.9%)
Progressed ≥ 2 steps	10 (9.9%)	1 (1.0%)	5 (4.9%)
Missing	12 (11.9%)	8 (7.8%)	10 (9.7%)
No Post-baseline	1	0	0
Cannot grade at baseline only	4	2	4
Cannot grade at last visit only	4	5	5
Cannot grade at baseline and last visit	3	1	1
Discontinued prior to Month 24	25	18	18
DR Severity Scale Change; n (%) [2]			
Improved ≥ 3 steps	0 (0%)	0 (0%)	0 (0%)
Improved ≥ 2 steps	1 (4.0%)	4 (22.2%)	3 (16.7%)
Progressed ≥ 3 steps	0 (0%)	0 (0%)	0 (0%)
Progressed ≥ 2 steps	0 (0%)	0 (0%)	0 (0%)
Missing	7 (28.0%)	4 (22.2%)	5 (27.8%)
No Post-baseline	3	1	4
Cannot grade at baseline only	2	0	1
Cannot grade at last visit only	0	2	0
Cannot grade at baseline and last visit	2	1	0

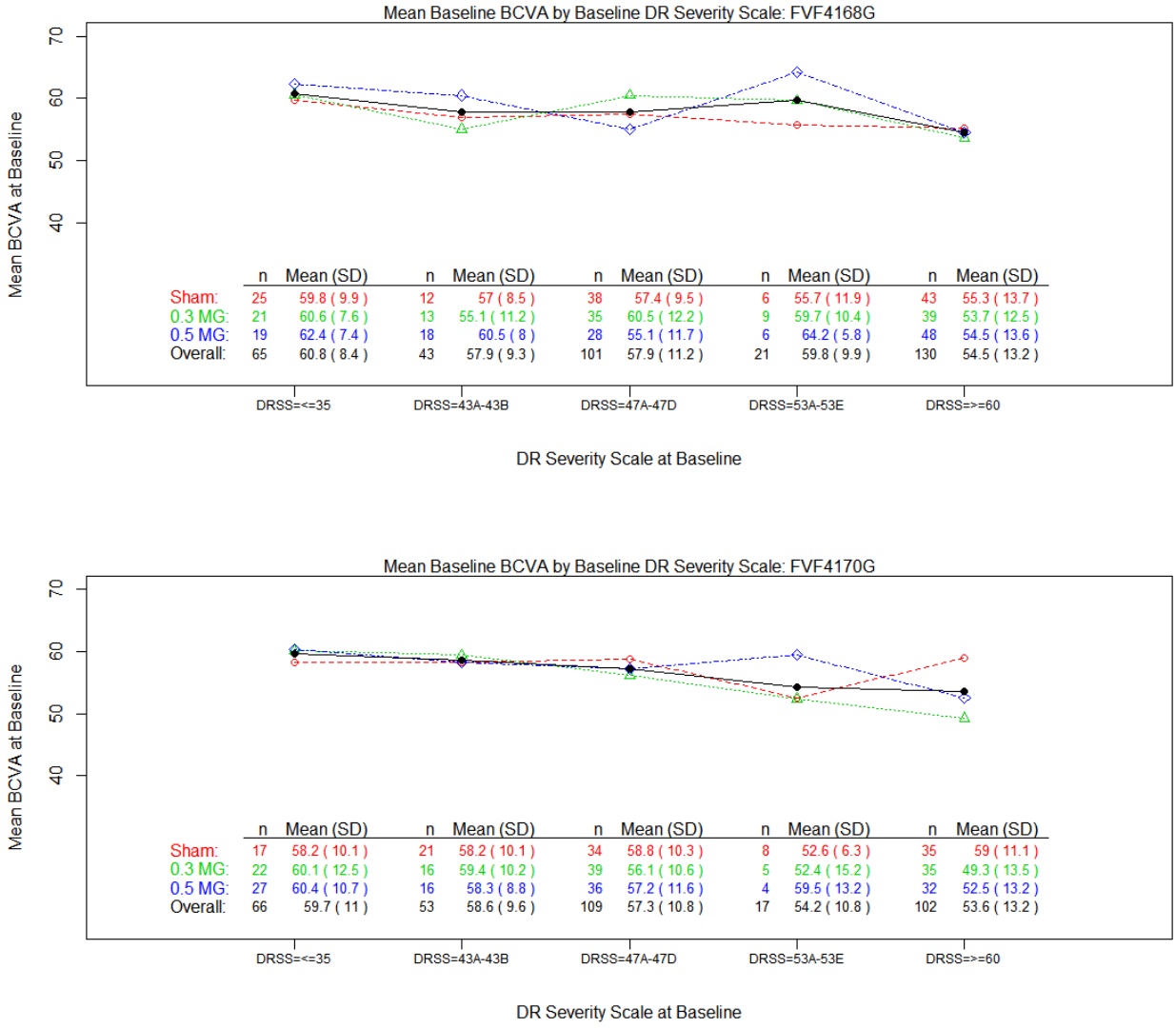
[1] The denominator is the number of subjects who completed follow-up through Month 24.
[2] The denominator is the number of subjects who discontinued prior to Month 24.
Source: Reviewer's analysis.

1.4.4.2 Visual Acuity and DR Severity Improvement/Progression

We examined the relationship between the DR severity improvement (2-step and 3-step) with the change in BCVA. The relation between the DR severity progression (2-step and 3-step) with the change in BCVA was not evaluated because only few subjects experienced 2-step or 3-step progression.

At baseline (Figure 6), subjects who had a higher DR severity scale tended to have lower BCVA score.

Figure 6: Plot of Mean Baseline BCVA by Baseline DR Severity Scale (Randomized Subjects with a Gradable Baseline DR Score)

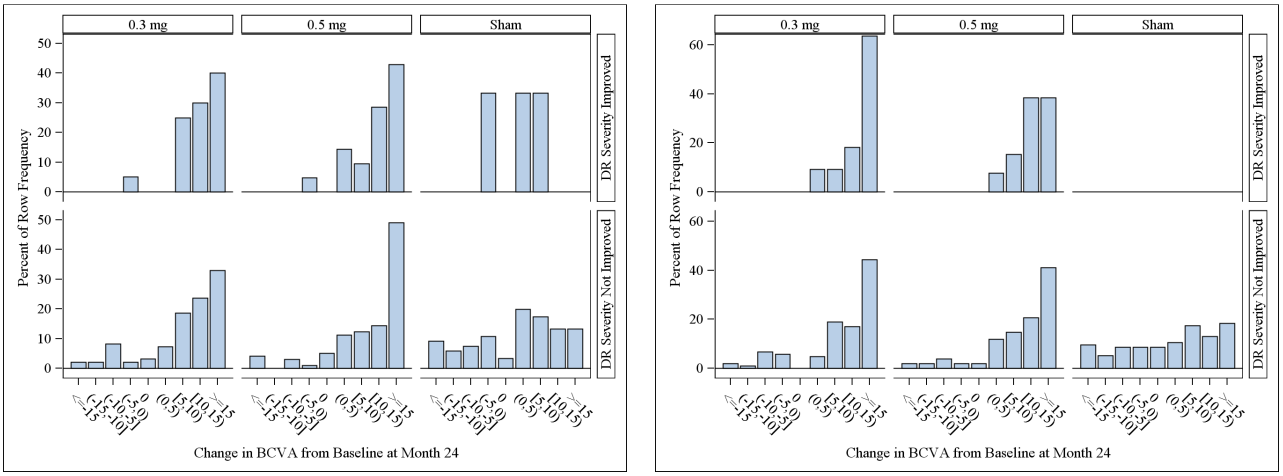


Source: Reviewer's analysis with assistance of Dr. Solomon Chefo.

The majority of subjects who had a 3-step improvement in DR severity (Figure 7, top row) experienced improvement in visual acuity; subjects who had a 2-step improvement in DR severity (Figure 8) were less likely to experience a loss in visual acuity. However, many subjects experienced improvement in visual acuity despite the lack of improvement in their DR severity.

Figure 7: Change in BCVA versus 3-step Improvement in DR Severity Scale from Baseline at Month 24 (Randomized Subjects with a Gradable DR Severity Score at Baseline; LOCF)

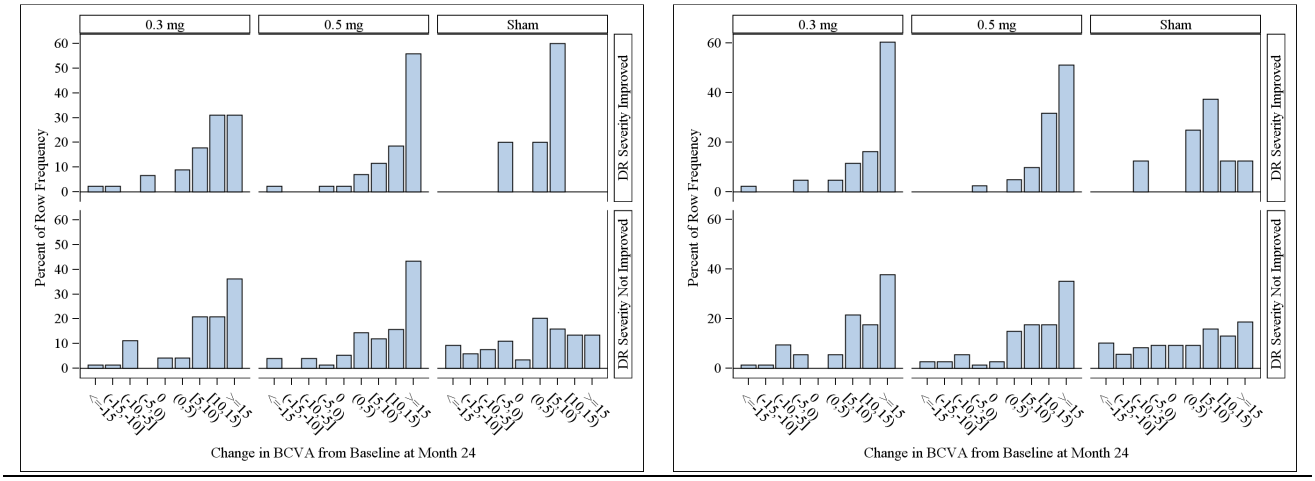
Study FVF4168g **Study FVF4170g**



Source: Reviewer's analysis.

Figure 8: Change in BCVA versus 2-step Improvement in DR Severity Scale from Baseline at Month 24 (Randomized Subjects with a Gradable DR Severity Score at Baseline; LOCF)

Study FVF4168g **Study FVF4170g**



Source: Reviewer's analysis.

1.4.4.3 Progression from NPDR to PDR

Table 13 presents the proportion of subjects who progressed to PDR at Month 24. The development of PDR was determined from the monthly indirect ophthalmoscopy assessment and was defined by the presence of neovascularization on the optic disc, elsewhere on the retina, or iris. A subject was considered to have progressed to PDR by a certain time point if

neovascularization was not present at baseline and emerged at any post-baseline visit at or prior to that time point. The assessment of the progression to PDR has clinical importance, because the transition from NPDR to PDR marks the point in DR progression when the disease requires destructive interventions with PRP or vitrectomy. As such, a DR treatment that slows the DR progression would reduce the need for PRP or vitrectomy procedure.

A significantly lower proportion of ranibizumab-treated subjects compared with control subjects progressed to PDR in both studies at Month 24. In Study FVF4168g, 3.2% of subjects in the 0.3 mg and 3.9% of subjects in the 0.5 mg groups had progressed to PDR compared with 11.5% of subjects in the sham group ($p = 0.0069$ and $p = 0.0206$ for 0.3 mg and 0.5 mg group vs. sham, respectively) by Month 24. In Study FVF4170g, 1.6% and 5.6% of subjects in the 0.3 mg and 0.5 mg groups had progressed to PDR compared with 15.0% of subjects in the sham group ($p = 0.0001$ and $p = 0.0114$ for 0.3 mg and 0.5 mg group vs. sham, respectively) by Month 24. The low percentages of subjects who had progressed to PDR in the ranibizumab groups by Month 24 were maintained through Month 36.

Table 13: Proportion of Subjects Progressing to PDR as Determined by the Indirect Ophthalmoscopy Assessment at Month 24 (Randomized Subjects)

	Treatment		
	Sham	**0.3 mg Ranibizumab**	**0.5 mg Ranibizumab**
Study FVF4168g			
N	130	125	127
Progression to PDR; n (%)	15 (11.5%)	4 (3.2%)	5 (3.9%)
Difference (95% CI) [a]		-9.1% (-15.4%, -2.7%)	-7.8% (-14.1%, -1.4%)
p-value [b]		0.0069	0.0206
Study FVF4170g			
N	127	125	125
Progression to PDR; n (%)	19 (15.0%)	2 (1.6%)	7 (5.6%)
Difference (95% CI) [a]		-13.6% (-20.2%, -7.0%)	-9.8% (-17.0%, -2.6%)
p-value [b]		0.0001	0.0114
Pooled			
N	257	250	252
Progression to PDR; n (%)	34 (13.2%)	6 (2.4%)	12 (4.8%)
Difference (95% CI) [a]		-11.0% (-15.5%, -6.5%)	-8.4% (-13.2%, -3.6%)
p-value [b]		<0.0001	0.0010

Note: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA1c (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] Weighted estimates adjusted for the baseline strata using Cochran-Mantel-Haenszel weights and normal approximation of the weighted estimates.

[b] From Cochran-Mantel-Haenszel chi-square tests adjusted for the baseline strata.

Source: Integrated Summary of Efficacy, Table 17.

1.5 Evaluation of Safety

The safety analyses of the two Phase III studies were previously submitted as part of the ranibizumab sBLA for the DME application. No further safety analyses were conducted in this sBLA submission (b) (4)

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were performed for the proportion of subjects with a ≥ 3-step improvement from baseline in ETDRS DR severity score at Month 24 by categories of the following demographic and baseline variables:

- age (<65 vs. ≥65 years),
- sex,
- race (White vs. Black or African American vs. other),
- HbA1c (≤8% vs. >8%),
- BCVA score (≤55 vs. >55 letters),
- prior therapy for DME (yes vs. no),
- baseline ETDRS DR severity scale (>35, <60, ≥60).

The subgroup analyses used the pooled data from Studies FVF4168g and FVF4170g. The percentage of subjects with a ≥ 3-step improvement from baseline in ETDRS DR severity score at Month 24 was higher in male subjects (17.3% for 0.3 mg ranibizumab and 17.2% for 0.5 mg ranibizumab) than in female subjects (7.4% for 0.3 mg ranibizumab and 11.0% for 0.5 mg ranibizumab). Otherwise, the treatment effect of either dose of ranibizumab vs. sham injection within the subgroups examined was generally consistent with the overall results at Month 24.

The percentages of subjects with a ≥ 3-step improvement in ETDRS DR severity score from baseline at Month 24 are presented in Appendix.

5 SUMMARY AND CONCLUSIONS

The results of the main analysis presented in this submission showed that a higher proportion of subjects in the ranibizumab-treated groups experienced a ≥ 3-step improvement in ETDRS DR severity score compared with the sham group at Month 24. As it was observed in both studies, a ≥ 3-step improvement may mean reversal of DR from high-risk PDR to mild NPDR for some patients (Figure 3 and Figure 4). Therefore, ranibizumab treatment would reduce the risk of developing vision threatening complications and decrease the need for invasive interventions, such as PRP and vitrectomy.

The beneficial effects of ranibizumab treatment compared with sham observed in the main analysis were supported by the analyses of other DR outcome measures at Month 24 and at other time points during the initial 2-year treatment period. The treatment benefits of ranibizumab were observed as early as Month 6 and the benefits at Month 24 were maintained at Month 36. When the results for subjects initially randomized to ranibizumab were compared with those for subjects who were randomized to sham during the initial treatment periods and crossed over to

treatment with ranibizumab at Month 25, early treatment was associated with better DR outcomes.

The protocols defined the proportion of subjects who achieved a ≥ 3-step progression from baseline in the DR severity scale at 24 months as a secondary efficacy endpoint. Although a favorable trend was observed for ranibizumab treatment in slowing DR progression, statistical significance was not demonstrated in the individual studies for the comparison of 0.3 mg ranibizumab group with the sham group with respect to this DR endpoint. This could be attributed to the low incidence of ≥ 3-step progression from baseline in the DR severity scale. In Studies FVF4168g and FVF4170g, approximately 5% of the subjects in the sham group and less than 2% of the subjects in the ranibizumab groups experienced a ≥ 3-step progression. The studies did not have sufficient number of subjects to demonstrate statistically significant difference between sham and ranibizumab groups. However, the treatment effect observed in this secondary efficacy endpoint demonstrated the potential utility of ranibizumab treatment in improving DR severity.

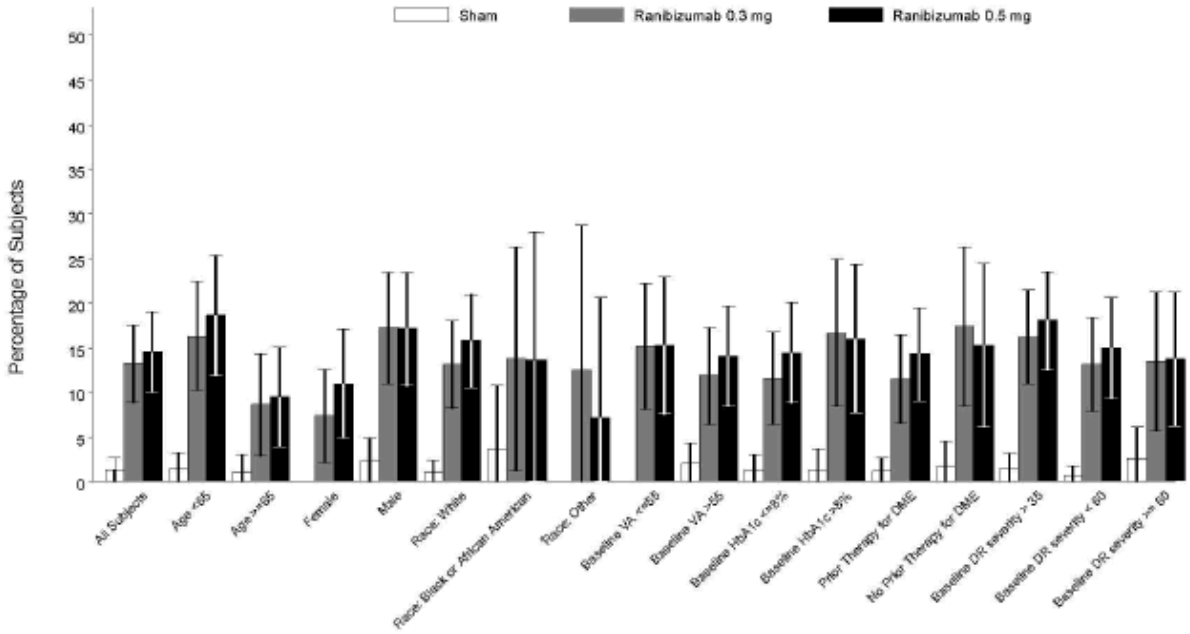
Although an improvement of ≥ 3-step in the DR severity scale was not a pre-specified endpoint in the study protocols, an improvement in the DR severity scale was considered a valid measurement for the clinical benefit of DR therapy. In the clinical studies of another anti-VEGF product for the same indication, the DR endpoint was defined as the proportion of the subjects who experienced an improvement of ≥2 steps in the DR severity scale.

The proportion of the subjects who achieved improvement in the DR severity tended to be higher than the proportion of the subjects who experienced progression in the DR severity; thus providing better chance to demonstrate statistical significance between treatment groups. The p-values from comparing ranibizumab treatment groups and the sham group with respect to an improvement of ≥ 3-step in the DR severity scale were <0.01 in both studies. These low p-values support the notion that the observed benefits of ranibizumab in the treatment of DR were unlikely due to chance alone.

In my view, the analyses of the data from Studies FVF4168g and FVF4170g demonstrated the benefits of ranibizumab in the treatment of DR in subjects with DME. A description of the study findings in the Lucentis USPI is informative for prescribing physicians. Section 14.4 of the label described the DR clinical studies and study results. We agree including Table 7 but suggest expand it to include the [redacted (b) (4)]. However, we recommend removal of Figure 7 from the label. [redacted (b) (4)] Because the clinical relevance of this endpoint is not clear to the statistical reviewer, we defer to the clinical team to determine if it is appropriate to include [redacted (b) (4)] in the label.

Appendix

Figure 9: Subgroups Analysis for the Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye at Month 24 (Studies FVF4168g and FVF4170g Pooled; Randomized Subjects with a Gradable DR Severity Score at Baseline; LOCF Method)



Source: Integrated Summary of Efficacy, Figure 29.

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/s/

DONGLIANG ZHUANG
01/15/2015

YAN WANG
01/15/2015
Concur with overall conclusions and see my secondary review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number:	Applicant:	Stamp Date:
125156/S106	Genentech, Inc.	August 7, 2014
Drug Name:	**NDA/BLA Type:**	**Indication:**
Lucentis® (ranibizumab injection)	sBLA, Priority Review	(b) (4)

On **initial** overview of the NDA/BLA application for refuse to file (RTF):

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			

We don't anticipate any review issues to be forwarded to the Applicant for the 74-day letter.

Dongliang Zhuang
Reviewing Statistician Date

Yan Wang
Supervisor/Team Leader Date

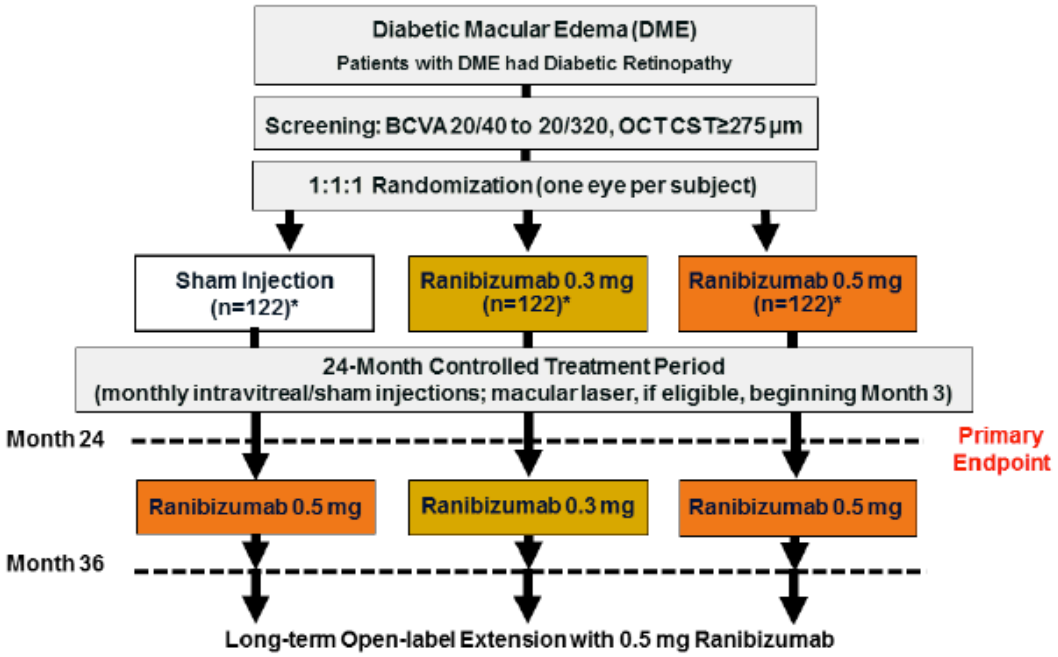
STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Appendix: Brief Summary of the Submission

The purpose of this supplemental BLA is to support a revision of the Lucentis U.S. Prescribing Information (USPI) to include a new indication (b) (4)

The proposed USPI revisions are based on the analyses of the safety and efficacy results from Studies FVF4168g and FVF4170g. These two studies supported the marketing approval of ranibizumab for the treatment of DME. They were identically designed Phase III, double-masked, multicenter, randomized, sham injection-controlled studies of the efficacy and safety of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus. The study design is shown in Figure 1.

Figure 1: FVF4168g and FVF4170g Study Design



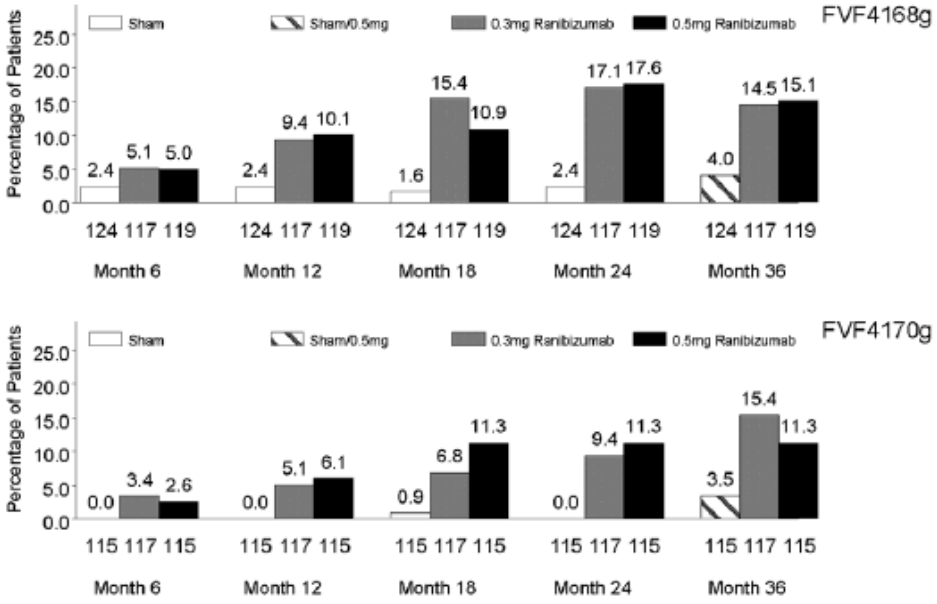
* Target enrollment.

All enrolled subjects in Studies FVF4168g and FVF4170g had DME and DR at baseline and represent the continuum of DR severity levels commonly observed in patients in clinical practice. Although the studies were designed to evaluate the effects of ranibizumab on outcome measures associated with DME, they also followed the improvement or worsening of DR on the validated ETDRS DR severity scale, as assessed from fundus photographs (FP) obtained at pre-specified timepoints and evaluated by masked graders at an independent reading center.

The main DR analysis was the proportion of subjects with a ≥ 3-step improvement from baseline in DR severity on the validated ETDRS DR severity scale at Month 24 (sham-

controlled period). The results from each of the individual studies, FVF4168g and FVF4170g, consistently demonstrated substantial and clinically meaningful treatment benefit in the main efficacy outcome measure of the proportion of subjects with a ≥3-step improvement in ETDRS DR severity score as assessed by color FP (Figure 2).

Figure 2: Proportion of Subjects with ≥ 3-Step Improvement from Baseline in ETDRS DR Severity Score in the Study Eye Over Time (Studies FVF4168g and FVF4170g; Randomized Subjects with a Valid Score at Baseline; LOCF Method)



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/s/

DONGLIANG ZHUANG
09/15/2014

YAN WANG
09/15/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA:	**BLA 125-156 (SE-106)**
Submission Date:	**07 August 2014**
Drug Product:	**Lucentis® (ranibizumab) for intravitreal injection, 6 mg/mL**
Sponsor:	**Genentech, Inc.**
Submission Type:	**Efficacy Supplement** [redacted] **)**
OCP Reviewer:	**Gerlie Gieser, Ph.D.**
Team Leader:	**Philip M. Colangelo, Pharm.D., Ph.D.**

I. BACKGROUND

In this efficacy supplement, the sponsor is seeking approval of Lucentis® (ranibizumab) intravitreal injection for the treatment [redacted] based on previous clinical trials conducted in diabetic macular edema (DME) patients. The proposed dosing regimen of Lucentis® (0.3 mg or 0.05 mL of 6 mg/mL) monthly for the [redacted] is the same as that already approved for the treatment of DME. No new serum pharmacokinetic data were submitted for review (apart for those already submitted and reviewed at the time of the NDA for the DME indication).

In addition, the sponsor proposed labeling changes (not specifically related to the new indication) under Section 12.3 Pharmacokinetics.

The focus of this Clinical Pharmacology review is the evaluation of the proposed labeling changes in Section 12.3 Pharmacokinetics, as shown below. (Sponsor's deleted text = strikethrough; added text = underscore)

"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)~~ [redacted] thought to be necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay [redacted]. No significant change was observed in the mean [redacted] plasma VEGF following [redacted] monthly 0.5 mg intravitreal injections. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 1 mg/eye. Serum ranibizumab concentrations in RVO, ~~and~~ DME and DR patients were similar to those observed in neovascular AMD patients."

The following three literature references were submitted to support the proposed labeling changes under Section 12.3:

- Yu L, Liang XH, Ferrara N. Comparing Protein VEGF inhibitors: In Vitro Biological Studies. *Biochem Biophys Res Commun* 2011;408:276-281
- Avery RL, Castellarin AA, Steinle NC, et al. Systemic Pharmacokinetics following Intravitreal Injections of Ranibizumab, Bevacizumab or Aflibercept in Patients with Neovascular AMD. *Br J Ophthalmol* 2014 ;Jul 7

- Wang X, Sawada T, Sawada O, Saishin Y, et al. Serum and Plasma Vascular Endothelial Growth Factor Concentrations Before and after Intravitreal Injection of Aflibercept or Ranibizumab for Age-Related Macular Degeneration. *Am J Ophthalmol* 2014;Jun 25

II. CLINICAL PHARMACOLOGY ASSESSMENT

1. (b) (4)

2. Based on the findings of Avery, et al (2014) (see Figures 3 and 4 of Appendix A of this review), the reviewer agrees with the addition of a labeling statement regarding the lack of a significant effect of 3 monthly intravitreal injections of Lucentis® 0.5 mg on baseline plasma VEGF concentrations of wet AMD patients. The reviewer's conclusion of "lack of significant effect on baseline VEGF concentrations" takes into consideration the HUVEC-derived ranibizumab IC_{50}

(11 to 27 ng/mL) for VEGF inhibition as defined in the Lucentis® USPI. The reviewer notes that in this paper, no evidence was provided to show that the plasma VEGF concentrations represented VEGF that was "free" (typically defined as unbound to plasma proteins), although techniques were employed in the study to minimize rupture of platelets that tend to sequester VEGF. The LLOQ of the VEGF assay was 10 pg/mL. Based on the findings of the AMD registration trials of Lucentis®, the visual acuity effect of ranibizumab leveled off after 3 monthly intravitreal injections. The reviewer also notes that this lack of a significant effect on baseline serum or plasma VEGF concentrations by intravitreally administered ranibizumab could explain (at least in part) the lack of a dose-related decrease in plasma VEGF concentrations (see Clinical Pharmacology review of the original BLA of Lucentis®).

3. The findings of Avery, et.al. (2014) were corroborated by the findings of a Japanese research group (Wang et al., 2014) which did not observe a significant change from baseline serum or plasma VEGF concentrations in treatment-naïve wet AMD patients following bimonthly intravitreal injections of ranibizumab 0.5 mg (Lucentis®; Novartis, Switzerland). See Figures 3 and 6 in Appendix B of thisreview. In the study conducted by Wang, the measured serum VEGF concentrations were numerically higher than those measured in the plasma; the LLOQ of the Human VEGF Quantikine® ELISA assay was 9.0 pg/mL. No ocular or systemic adverse events were observed during the 2-month observation period in Wang's study.

4. Note that per internal agreement, the Medical Officer and the Statistical Reviewer assigned to this application will evaluate the acceptability of the sponsor's proposed changes in Section 12.2 Pharmacodynamics since the statements are related to the use of a PD metric for diagnosis of disease severity and progression, and/or the primary efficacy outcomes of the clinical trials conducted by the sponsor.

5. Based on the dose-proportionality findings of the AMD-4 (HARBOR) trial, the upper bound of the linear dose range of serum ranibizumab concentrations could be extended from 1 mg/eye to 2 mg/eye (see Appendix C of this review).

III. LABELING RECOMMENDATIONS:

Note that the specific location of the sponsor's proposed labeling changes are marked with a yellow highlight. The reviewer's recommended labeling edits are either underscored (added text) or marked with a strikethrough (deleted text).

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 pathophysiology of neovascular AMD, macular edema following RVO, DR and DME. 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.

Reviewer's Note (not for sponsor): Defer to Medical Officer

12.2 Pharmacodynamics

Increased retinal thickness (i.e., center point thickness (CPT) or central foveal thickness (CFT)), as assessed by optical coherence tomography (OCT) is associated with neovascular AMD, macular edema following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD. Microvascular retinal changes, (b) (4) and neovascularization (b) (4) as assessed by color fundus photography, are associated with diabetic retinopathy.

Reviewer's Note (not for sponsor): Defer to Medical Officer

...

Diabetic Macular Edema

On average, CPT reductions were observed in Studies D-1 and D-2 beginning at Day 7 following the first LUCENTIS injection through Month 36. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.3)*].

(b) (4)

Improvements from baseline in DR severity as assessed on fundus photography were observed in Studies D-1 and D-2 at (b) (4) (first scheduled DR photographic assessment after randomization) through Month 36 [*see Clinical Studies (14.4)*].

Reviewer's Note (not for sponsor): Defer to Medical Officer

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 was more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration, the maximum ~~ranibizumab~~ serum ranibizumab concentrations were ~~low 0.3 ng/mL to 2.36 ng/mL~~ on average, 5.5 ng/mL. These ~~levels~~ concentrations were below the concentration range of ranibizumab (b) (4) 11 to 27 ng/mL) ~~thought to be~~ that was necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an *in vitro* cellular proliferation assay (based on (b) (4) human umbilical vein endothelial cells (HUVEC)). No significant change from baseline was observed in the mean (b) (4) -plasma VEGF concentrations following (b) (4) three monthly 0.5 mg intravitreal injections. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to ~~1~~ 2 mg/eye. Serum ranibizumab concentrations in RVO, DME and DR patients were similar to those observed in neovascular AMD patients.

Note to Sponsor: *The maximum serum ranibizumab concentration (0.3 ng/mL to 2.36 ng/mL) was updated to the mean value (0.11 nM = 5.5 ng/mL) as reported by Avery and coworkers (2014). We recommend that the current ranibizumab IC_{50} for VEGF inhibition (11 to 27 ng/mL) be retained until data based on a human retinal cell line become available for review.*

Based on the serum ranibizumab concentration data from the HARBOR trial, we are extending the range for dose proportionality of serum ranibizumab concentrations from 1 mg/eye to 2 mg/eye.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, 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.

In pharmacokinetic covariate analyses, 48% (520/1091) of patients had renal impairment (35% mild, 11% moderate, and 2% severe). Because the increases in plasma ranibizumab exposures in these patients are not considered clinically significant, no dosage adjustment is needed based on renal impairment status.

_____

Gerlie Gieser, Ph.D.
Office Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL) _____

Appendix A. Tables and Figures from Avery et al., 2014

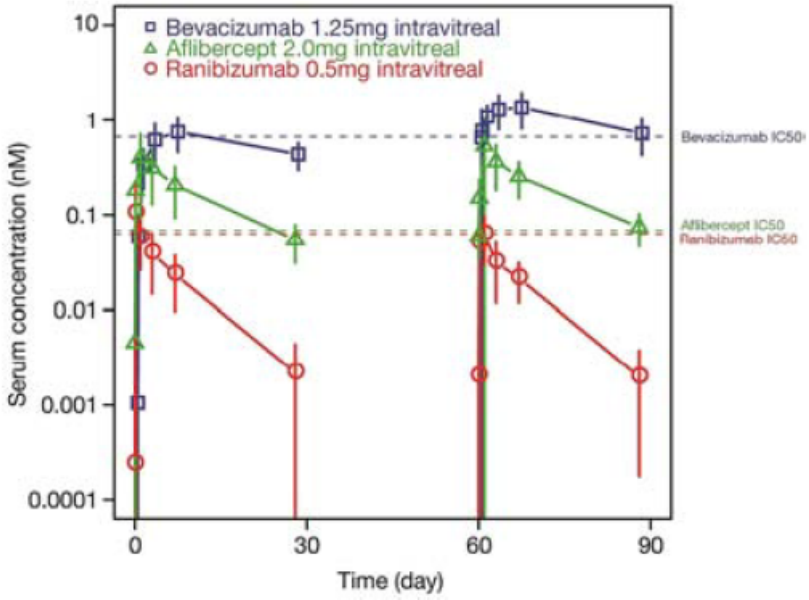

Figure 1 Serum concentration–time curves for ranibizumab, bevacizumab, or aflibercept following intravitreal injection in patients with age-related macular degeneration.

Table 1 Mean (SD) systemic exposures of bevacizumab, ranibizumab and aflibercept

				Geometric mean ratio	
	Bevacizumab	Ranibizumab	Aflibercept	Bevacizumab/ ranibizumab (95% CI)	Aflibercept/ ranibizumab (95% CI)
First dose					
C_{max}, nM	0.76 (0.31) n=15	0.11 (0.13) n=20	0.45 (0.29) n=21	8.80 (5.59 to 13.8)	4.65 (3.07 to 7.05)
C_{min}, nM	0.44 (0.14) n=14	0.002 (0.002) n=19	0.05 (0.02) n=20	310 (188 to 511)	37.3 (23.7 to 58.7)
AUC_{0-28}, nM*h	15.73 (5.76) n=14	0.46 (0.24) n=19	4.32 (1.77) n=20	34.9 (26.4 to 46.1)	9.49 (7.4 to 12.2)
Third dose					
C_{max}, nM	1.47 (0.55) n=15	0.07 (0.05) n=18	0.58 (0.52) n=21	22.7 (14.8 to 34.8)	7.28 (4.91 to 10.8)
C_{min}, nM	0.70 (0.29) n=14	0.002 (0.002) n=18	0.07 (0.03) n=21	500 (304 to 822)	52.9 (33.8 to 82.8)
AUC_{60-88}, nM*h	29.12 (10.35) n=14	0.41 (0.17) n=18	5.38 (1.77) n=21	72.4 (55.4 to 94.8)	13.5 (10.6 to 17.3)

AUC, area under curve; C_{max}, maximum serum concentration; C_{min}, minimum serum concentration.

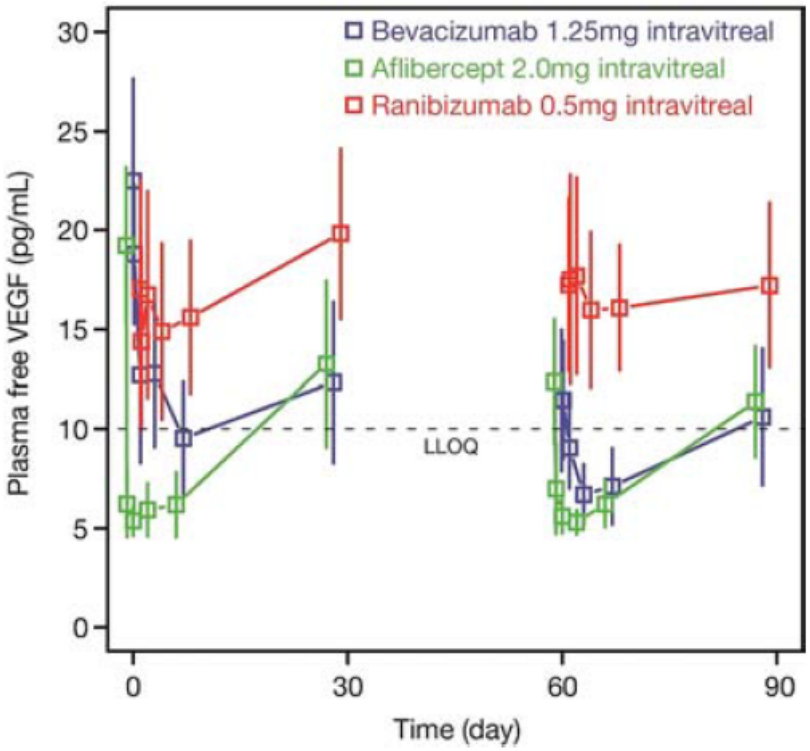

Figure 2 Mean (95% CI) plasma free VEGF concentration following intravitreal injection of ranibizumab, bevacizumab, or aflibercept in patients with age-related macular degeneration. VEGF, vascular endothelial growth factor.

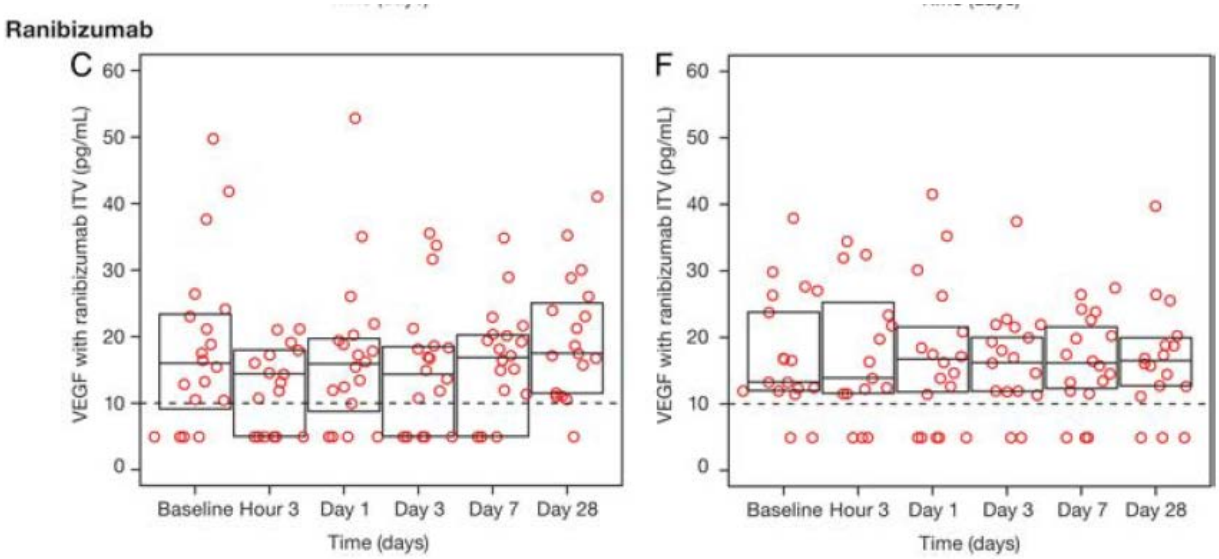

Figure 3. Individual observed plasma free VEGF concentrations following intravitreal injection of ranibizumab. ITV,intravitreal; VEGF, vascular endothelial growth factor.

Appendix B. Figures from Wang et al., 2014

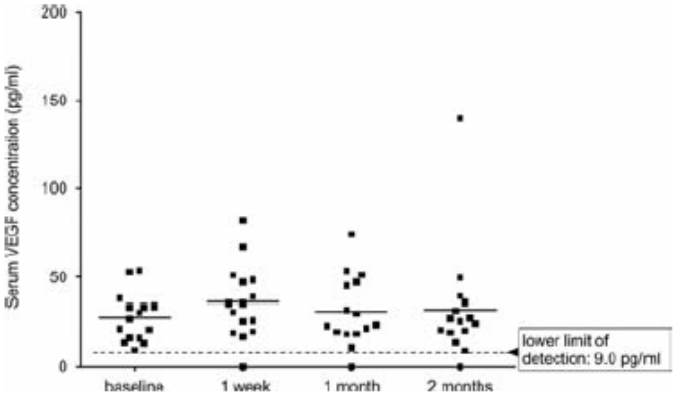

FIGURE 3. Scatterplot showing serum vascular endothelial growth factor (VEGF) concentration before and after intravitreal ranibizumab injection in the ranibizumab group. There was no significant difference among time points ($P = .36$).

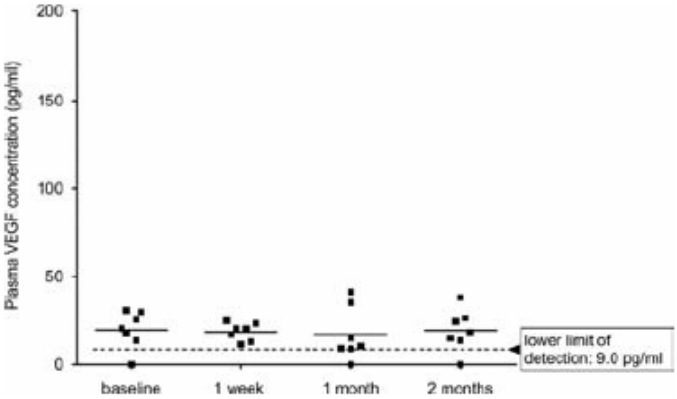

FIGURE 6. Scatterplot showing plasma vascular endothelial growth factor (VEGF) concentration before and after intravitreal ranibizumab injection in the ranibizumab group. There was no significant difference in plasma VEGF concentration between baseline and after intravitreal ranibizumab injection ($P = .93$).

Appendix C.

Serum Ranibizumab Concentrations in Pharmacokinetic Evaluable Patients in the HARBOR Trial

Ranibizumab Treatment Group	Number of Samples	LTR	Mean	SD	CV (%)	Geometric Mean	Median	Minimum	Maximum
0.5 mg monthly									
Screening	272	254 (93.4%)	NR	NR	NR	NR	LTR	LTR	33.600
Day 7	261	0	1.397	1.599	114.5	1.111	1.130	0.019	19.900
Month 2 (1–5 days post third dose)	70	0	1.724	1.067	61.9	1.104	1.770	0.019	4.880
Month 11 (9–21 days post 12th scheduled visit)	61	0	0.803	0.808	100.6	0.490	0.524	0.017	3.620
Month 12 (pre-injection)	245	28 (11.4%)	0.164	0.258	157.1	0.082	0.099	0.008	2.900
0.5 mg PRN									
Screening	274	251 (91.6%)	NR	NR	NR	NR	LTR	LTR	10.000
Day 7	259	0	1.272	0.766	60.2	1.089	1.160	0.024	6.470
Month 2 (1–5 days post third dose)	98	3 (3.1%)	1.866	1.554	83.3	1.027	1.700	0.008	10.800
Month 11 (9–21 days post 12th scheduled visit)	76	26 (34.2%)	NR	NR	NR	NR	0.335	LTR	45.400
Month 12 (pre-injection)	249	106 (42.6%)	NR	NR	NR	NR	0.092	LTR	15.800
2.0 mg PRN									
Screening	272	252 (92.6%)	NR	NR	NR	NR	LTR	LTR	23.700
Day 7	258	1 (0.4%)	4.933	2.850	57.8	4.124	4.550	0.008	22.300
Month 2 (1–5 days post third dose)	80	0	7.284	4.934	67.7	4.620	6.490	0.045	22.200
Month 11 (9–21 days post 12th scheduled visit)	63	14 (22.2%)	1.546	2.552	165.1	0.255	1.130	0.008	15.200
Month 12 (pre-injection)	247	104 (42.1%)	NR	NR	NR	NR	0.229	LTR	11.900
2.0 mg monthly									
Screening	273	252 (92.3%)	NR	NR	NR	NR	LTR	LTR	27.600
Day 7	258	0	5.106	3.199	62.7	4.324	4.395	0.016	26.000
Month 2 (1–5 days post third dose)	79	0	7.878	4.908	62.3	5.678	6.900	0.096	24.100
Month 11 (9–21 days post 12th scheduled visit)	59	1 (1.7%)	3.544	4.077	115.0	2.220	2.690	0.008	26.800
Month 12 (pre-injection)	249	5 (2.0%)	0.731	1.461	200.0	0.325	0.396	0.008	12.000

CV=coefficient of variation; LTR=less than reportable (< 0.015 ng/mL); NR=Non-reportable. LTR values at Screening were set to 0. All other LTR values were handled as follows: For a given treatment and sampling day, if one-third or fewer values were LTR, the LTR values were set to 0.0075 ng/mL, which is half of the limit of quantitation, and all summary statistics were computed. If more than one-third but less than one-half of the values were LTR, only the median, 75th percentile, and maximum were calculated and the rest of the summary statistics were either LTR or NR. If one-half or more values were LTR, then only 75th percentile, and maximum were calculated and the rest of the summary statistics were either LTR or NR. Samples obtained at the following timepoints were optional from patients who provided consent: 1–5 days after third dose (Month 2), 9-21 days after 12th scheduled visit (Month 11).

Source: NDA 125-156 (S-081)

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/s/

GERLIE GIESER
10/16/2014

PHILIP M COLANGELO
10/16/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**BLA 125-156 (SE-106)**	**Brand Name**	**Lucentis®**
OCP Division (I, II, III, IV, V)	**DCP4**	**Generic Name**	**ranibizumab**
Medical Division	**DTOP**	**Drug Class**	**VEGF inhibitor**
OCP Reviewer	**Gerlie Gieser, PhD**	**Indication(s)**	**(b) (4)**
OCP Team Leader	**Philip Colangelo, PharmD, PhD**	**Dosage Form**	**injection**
Pharmacometrics Reviewer	-	**Dosing Regimen**	**0.3 mg (0.05 mL of 6 mg/mL) every 28 days**
Date of Submission	**07 August 2014**	**Route of Administration**	**For intravitreal injection**
Estimated Due Date of OCP Review	**13 January 2015**	**Sponsor**	**Genentech**
Medical Division Due Date	**TBD**	**Priority Classification**	**Priority**
PDUFA Due Date	**06 February 2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**			**2 literature studies (effect on serum VEGF concentrations)**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**			**PD markers of DR severity and progression**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies	**5**			**2 Phase 3 trials + 3 literature references supporting labeling changes in Section 12.3 of USPI**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			dose evaluated in Ph 3 trials
6	Is the clinical pharmacology and biopharmaceutics section of the NDA	X			as related to PD endpoints

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

	organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			as related to PD endpoints
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	serum PK already evaluated in DME patients (same patients with DR in the same Ph 3 trials)
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			two Lucentis IVT doses evaluated in Phase 3 trials
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the			X	not specifically relevant to the (b) (4)

	pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				(b) (4): Three literature studies submitted to support changes in IC_{50} needed for VEGF inhibition *in vitro* (using BREC rather than HUVEC cell line), and effect on human serum VEGF concentrations (USPI Section 12.3)
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			DR severity/progression being linked to PD changes in retinal anatomy as assessed via fundus photography, etc. in Phase 3 trials
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Gerlie Gieser, PhD — 02 September 2014
Reviewing Clinical Pharmacologist — Date

Philip Colangelo, PharmD, PhD
Team Leader/Supervisor — Date

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/s/

GERLIE GIESER
09/11/2014

PHILIP M COLANGELO
09/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 16, 2015

To: Christina Marshall, M.S., Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA #125156/ S-106
Lucentis® (ranibizumab injection)

As requested in your consult dated October 28, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the proposed draft labeling for Lucentis® (ranibizumab injection).

We note that S-106 concerns the addition of an [redacted] (b) (4)

OPDP's comments are based on the substantially complete version of the PI titled, "sBLA 125156_106 clean-label-text.doc" which was received via email from DTOP on January 15, 2015.

OPDP's comments are attached in the marked-up substantially complete version of the labeling.

Thank you for the opportunity to provide comments on this proposed PI.

If you have any questions about OPDP's comments, please contact Christine Corser at 6-2653 or at christine.corser@fda.hhs.gov.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE G CORSER
01/16/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: sBLA 125156/106

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Lucentis (ranibizumab injection)

Applicant: Genentech, Inc.

Receipt Date: August 7, 2014

Goal Date: February 7, 2015

1. Regulatory History and Applicant's Main Proposals

Genentech's proposed revisions are based on detailed analyses of the safety and efficacy results from two studies; FVF4168g and FVF4170g, each entitled, "A Phase III, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus." The results from these studies provided a basis (b) (4)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

YES 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA D MARSHALL
01/15/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
BLA# 125156	BLA Supplement # 106	Efficacy Supplement Type SE-
Proprietary Name: Lucentis Established/Proper Name: ranibizumab for injection Dosage Form: injection Strengths: 0.5mg		
Applicant: Genentech, Inc. Agent for Applicant (if applicable):		
Date of Application: August 7, 2014 Date of Receipt: August 7, 2014 Date clock started after UN:		
PDUFA Goal Date: February 7, 2015	Action Goal Date (if different): February 6, 2015	
Filing Date: October 6, 2014	Date of Filing Meeting: September 15, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of patients with diabetic retinopathy (DR).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☒ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 8633	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	sBLA
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☐	☒	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	sBLA
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Efficacy supplement no new CMC information submitted.
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☒	☐	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	Waiver included
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☐	☒	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** May 20, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 15, 2014

BLA/NDA/Supp #: 125156/S-106

PROPRIETARY NAME: LUCENTIS

ESTABLISHED/PROPER NAME: ranibizumab for injection

DOSAGE FORM/STRENGTH: injection, 0.5mg

APPLICANT: Genentech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): (b) (4)

BACKGROUND: Genentech's proposed revisions are based on detailed analyses of the safety and efficacy results from two studies; FVF4168g and FVF4170g, each entitled, "A Phase III, Double-Masked, Multicenter, Randomized, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus." The results from these studies provided a basis (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christina Marshall	Y
	CPMS/TL:	Judit Milstein	Y
Cross-Discipline Team Leader (CDTL)	William M. Boyd		Y
Clinical	Reviewer:	Rhea Lloyd	Y
	TL:	William M. Boyd	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Gerlie Gieser	Y
	TL:	Philip Colangelo	N
Biostatistics	Reviewer:	Dongliang Zhuang	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Maria Rivera	Y
	TL:	Lori Kotch	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	Chen Sun	Y
	TL:	Michele Dougherty	Y
Product Quality (CMC)	Reviewer:	Chen Sun	Y
	TL:	Michele Dougherty	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Renata Albrecht, Wiley Chambers.		

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☒ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: This supplement provides for re-analysis of originally submitted data. Site Inspections were done previously	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Christina Marshall

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones

Comments: Mid-Cycle Meeting: October 30, 2014
Wrap-up Meeting: January 9, 2014

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	BLA/BLA supplements: If filed, send 60-day filing letter

☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☒	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA D MARSHALL
10/20/2014
sBLA Filing Review

JUDIT R MILSTEIN
12/05/2014

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Transplant and Ophthalmology Products
December 1, 2014

Summary Box

1. IND 8633
2. Genentech, Inc.
3. Lucentis (ranibizumab injection)
4. Treatment of diabetic retinopathy in patients with diabetic macular edema
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition?

   Yes.
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints?

   Yes. A supplement for this indication has already been submitted. There is currently no approved treatment for patients with diabetic retinopathy. The clinical evidence from two clinical studies with 24 months of controlled treatment demonstrates that Lucentis (ranibizumab injection) provides a statistically significant improvement in both a ≥ 2-step and ≥ 3-step improvement (on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale) in patients with diabetic macular edema and diabetic retinopathy.

1. Brief description of the drug

Lucentis (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment for intraocular use. Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF110. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, and DME. 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 cell proliferation, vascular leakage, and new blood vessel formation.

Lucentis (ranibizumab injection) has been approved for the treatment of neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO) and diabetic macular edema (DME).

2. Brief description of the disease and intended population

Diabetic retinopathy is a common microvascular complication of diabetes. In the US, diabetic retinopathy (DR) is a serious disease and is the leading cause of vision loss and blindness in the

population of working age adults 20-74 years of age.[1] It accounts for 8% of all cases of legal blindness and 12% of newly blind patients. The incidence of DR in patients increases with the duration of the disease, eventually affecting most diabetic patients. Also, according to the CDCP, in 2005-2008 nearly one-third of Americans aged 40 and older living with diabetes developed DR, and 4.4% (approximately 655,000) had an advanced vision threatening form of DR.[1] Progression of non-proliferative DR (NPDR) to Proliferative Diabetic Retinopathy (PDR) is a serious and clinically significant progression of the disease pathology, and marks the transition to advanced disease. PDR is associated with a high risk of visual morbidity including vitreous hemorrhage, traction retinal detachment and neovascular glaucoma.[2] Preventative treatment of patients with pre-proliferative DR has been pan-retinal photocoagulation (PRP also known as laser therapy), a procedure which destroys peripheral retinal tissue in order to salvage the macula which provides sharpest visual acuity. PRP may also cause significant morbidity.

Diabetic retinopathy is measured in discrete steps. The Early Treatment Diabetic Retinopathy Study (ETDRS) diabetic retinopathy severity scale was first described and validated in 1991 in a 5 year, multicenter trial supported by NIH. The scale is an objective quantification of retinopathy severity and a validated method for quantifying changes in DR.[2, 3, 4, 5]

International Clinical Diabetic Retinopathy Disease Severity Scale (DRSS)

DRSS Level	Description
10	DR absent
20	Microaneurysms only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53	Severe NPDR
60,61	Mild PDR
65	Moderate PDR
71	High Risk PDR
75	High Risk PDR
81	Advanced PDR, fundus partially obscured, center of macula attached
85	Advanced PDR, posterior fundus obscured or center of macula detached
90	Cannot grade, even sufficiently for level 81 or 85

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

The endpoints proposed by the sponsor for the breakthrough designation are the following:

- the proportion of patients treated with ranibizumab 0.3 mg compared to sham who achieved DR improvement ≥ 2 step improvement on the DRSS scale at Month 24 and;

- the proportion of patients treated with ranibizumab 0.3 mg compared to sham who achieved DR improvement of ≥ 3 step improvement on the DRSS scale at Month 24.

The Division accepts the following endpoints for the indication of diabetic retinopathy:

- proportion of patients with a ≥ 2 step improvement or ≤ 2 worsening on the DRSS scale in a single study eye* at week 52 or longer for patients with NPDR at baseline.
- proportion of patients with a ≥ 3 step improvement or ≤ 3 worsening on the DRSS scale in a combination of both eyes* at week 52 or longer for patients with NPDR at baseline.
- ≥ 3 step change in visual acuity on the ETDRS chart at week 52 or longer for patients with NPDR at baseline

*When a single eye is enrolled in a clinical trial, a 2 step change on the DRSS scale is considered clinically significant. When both eyes are enrolled, a total of 3 steps is considered clinically significant (i.e. 2 step in one eye, 1 step in the other eye or 3 steps in one eye, no change in the other eye)

4. Brief description of available therapies (if any)

There are currently no drugs/biologics approved for the treatment of diabetic retinopathy. Currently, the management of DR consists of:

- Systemic approaches during the early stages of DR. They include early detection, life-style changes and optimal control of hyperglycemia, hyperlipidemia, and hypertension.
- Surgical/laser approaches for the advanced stages of DR. They include pan-retinal photocoagulation (PRP) and vitreous surgery.

The existing therapies for DR (e.g., early detection and metabolic control or PRP and vitreous surgery for the advanced stages of DR) work to slow down the worsening of DR and sometimes have serious side effects such as surgical complications or substantially reduced visual function due to laser scarring. A treatment that results in a robust DR improvement, represents a major advance in the management of DR. Therefore, there is a need for therapies like ranibizumab.

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

Eylea (aflibercept) is being studied for this same indication, and has received breakthrough therapy designation. A supplement for this indication has recently been submitted. These two biologic products belong to the same class (growth factor inhibitors) and have similar regulatory histories. A preliminary review of the data indicate that the two biologic products have a similar treatment effect on diabetic retinopathy.

6. Description of preliminary clinical evidence

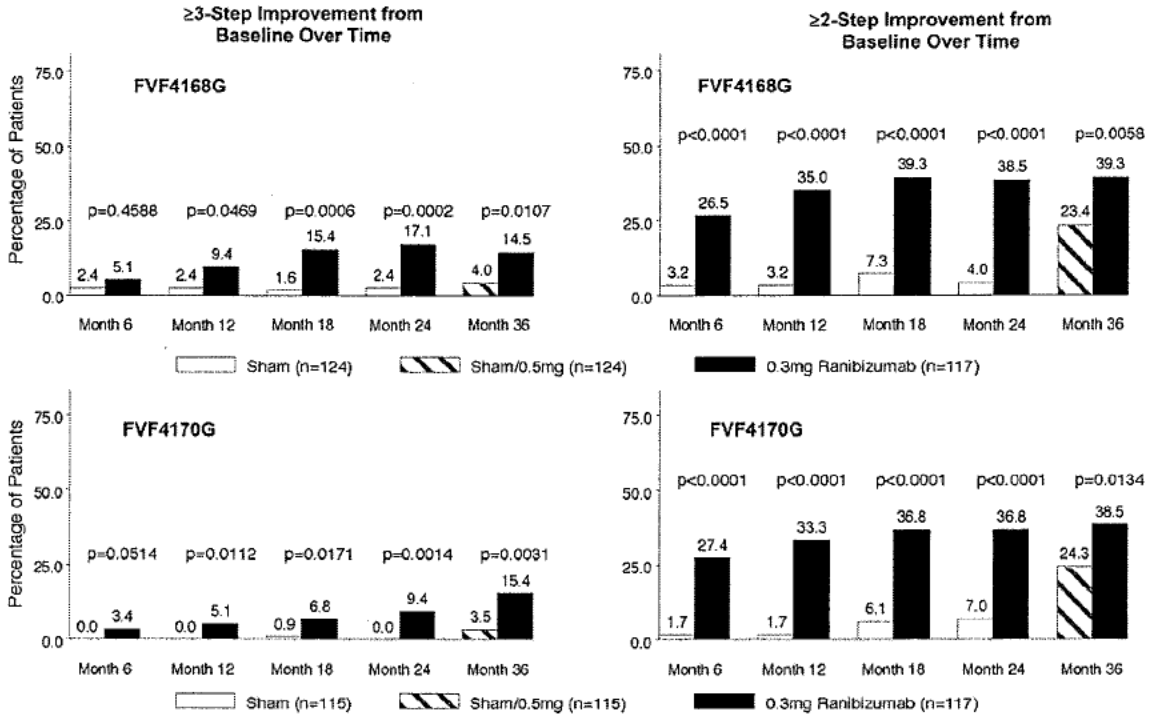
The breakthrough request is based on the results of Studies FVF4168g and FVF4170g, identically designed Phase 3, double-masked, multicenter, randomized, sham injection-controlled studies of the efficacy and safety of monthly 0.3 mg or 0.5 mg ranibizumab injection in patients with clinically significant macular edema with central involvement (CSME-CI) secondary to diabetes mellitus (Type 1 or 2), which were run in parallel. All enrolled patients had DR and DME at baseline. The studies were controlled for the first 24-months. Beyond Month 24, patients in the sham group were crossed over to the ranibizumab 0.5 mg group for 12 additional months. An optional open-label extension was conducted through Month 60. The primary endpoint was the proportion of subjects gaining ≥ 15 letters from baseline in best corrected visual acuity (BCVA) score in the study eye at 24 months.

The studies were successful and the supplement was approved for the treatment of DME. Both studies included as a secondary endpoint, the percentage of patients with a 3 step or more *worsening* on the DRSS scale. For this secondary endpoint, the p-value in one study was p=0.0073 and in the other was 0.2721. (b) (4)

The applicant subsequently discovered that the percentage of patients with a 3-step or more *improvement*, favored the ranibizumab group (unadjusted p value of 0.0001 in each trial).

Efficacy Results for the Diabetic Retinopathy

Figure 1 Proportion of Patients with ≥ 3-Step and ≥ 2-Step Improvement from Baseline in ETDRS Diabetic Retinopathy Severity Level over Time in Study FVF4168g and Study FVF4170g.



7. Division's recommendation and rationale

While a full clinical review is ongoing, preliminarily, the clinical evidence submitted supports the addition of a diabetic retinopathy indication in patients with diabetic macular edema. Lucentis if approved may provide an effective treatment for diabetic retinopathy in patients with diabetic macular edema for which there are no currently approved treatments.

The Division agrees that Lucentis meets the criteria for breakthrough therapy.

8. Division's next steps and sponsor's plan for future development

The Division will complete the ongoing review of the efficacy supplement currently in-house (PDUFA goal date February 6, 2015).

9. References (if any)

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2014: Estimates of Diabetes and Its Burden in the United States. Atlanta, FA: US National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention [resource on the internet; cited July 2014]. Available at: http://www.cdc.gov//diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
2. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the Diabetic Retinopathy Study. The Diabetic Retinopathy Study Research Group. Arch Ophthalmol 1979; 97:654-5.
3. Klein et al. Medication use and the 5-year incidence of early age-related maculopathy: the Beaver Dam Eye Study. Arch Ophthalmol 2001 Sep; 119:1354-9.
4. American Academy of Ophthalmology Retinal/Vitreous Preferred Practice Pattern Panel, Hoskins Center for Quality Eye Care. Guidelines: diabetic retinopathy PPP-2012. Available at: http://one.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp-september-2008-4thprint.
5. Grading diabetic retinopathy from stereoscopic color fundus photographs – an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98(5 Suppl):786-806.

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/s/

SANDRA J BENTON
11/24/2014

WILEY A CHAMBERS
11/25/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125156Orig1s106

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125156 | Supplement Number: 106 | NDA Supplement Type (e.g. SE5): Efficacy

Division Name: DTOP | PDUFA Goal Date: 2/6/15 | Stamp Date: 8/7/2014

Proprietary Name: Lucentis

Established/Generic Name: ranibizumab

Dosage Form: injection 0.3mg

Applicant/Sponsor: Genentech

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Neovascular (wet) Age-Related Macular Degeneration(AMD)
(2) Macular Edema Following Rentinal Vein Occulusion (RVO)
(3) Diabetic Macular Edema (DME)
(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 Diabetic Retinopathy (DR) in patients with DME (new indication)

Q1: 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.)

Section 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
- ☒ 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.

Section 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	0 yr. 0 mo.	16 yr. 11 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):

Additional 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	0 yr. 0 mo.	16 yr. 11 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.

Pediatric 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	0 yr. 0 mo.	16 yr. 11 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 appropriate 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.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Neovascular (wet) Age-Related Macular Degeneration(AMD)

Indication #3: Macular Edema Following Rentinal Vein Occulusion (RVO)

Indication #4: Diabetic Macular Edema (DME)

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☒ No. Please proceed to the next question.

Q2: 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.)

Section 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
  - ☒ 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.

Section 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 failedΔ
☐	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 Section 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 some or all 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	0 yr. 0 mo.	16 yr. 11 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):

Additional 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	0 yr. 0 mo.	16 yr. 11 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.

Pediatric 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	0 yr. 0 mo.	16 yr. 11 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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Attachment
Justification of All Indications

All of the above indications progress over years; disease management in newly diagnosed pediatric patients generally focuses on surveillance and prevention. The strategy to prevent RVO, AMD, and DME includes screening programs and regular follow-up with affected patients. These indications are rarely expressed at a level greater than background retinopathy during childhood and adolescence, and treatment is rarely required until the patient becomes an adult. In summary, the severity of RVO, AMD, and DME diagnosed in the pediatric population is mild and rarely warrants treatment. Therefore, management of these indications among pediatric patients is focused on surveillance and prevention. Those pediatric patients who do experience worsening beyond moderate and other associated complications may warrant surgical or laser therapy, similar to adults; however, this is rare.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA D MARSHALL
02/09/2015
sBLA 125156/106 Pediatric Page

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

BLA # 125156	BLA Supplement # 106	If NDA, Efficacy Supplement Type: Efficacy *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Lucentis Established/Proper Name: ranibizumab Dosage Form: injection		Applicant: Genentech Agent for Applicant (if applicable):
RPM: Christina Marshall		Division: DTOP

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☒ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is February 7, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☒ Breakthrough Therapy designation (Granted 12/14/14)
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: Genentech submitted a Breakthrough Designation request while supplement was already in house.

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	February 6, 2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included, February 5, 2015
• Original applicant-proposed labeling	☒ Included, August 7, 2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ January 15, 2015 DMEPA: ☐ None DMPP/PLT (DRISK): ☐ None OPDP: ☒ January 16, 2015 SEALD: ☐ None CSS: ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	December 5, 2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC December 3, 2014 If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Advice Information Request, 12/18/14 Filing Notification, 10/3/14
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	PeRC BPCA subcommittee mins, 12/22/14 MPC BTD mins, 11/25/14 PeRC PREA subcommittee mins, 11/17/14
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	July 17, 2013
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	February 6, 2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	February 6, 2015
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Concurred with primary review
• Clinical review(s) *(indicate date for each review)*	Primary Review 1/29/15 Filing Review 9/16/14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Medical Officer Primary review page 8

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	Secondary review 1/15/15
Statistical Review(s) *(indicate date for each review)*	Primary review 1/15/15 Filing review 9/15/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Concurred with primary review
Clinical Pharmacology review(s) *(indicate date for each review)*	Primary review 9/11/14 Filing Review 10/16/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review Concurred with primary review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Primary review 1/14/15 Filing review 1/21/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Concurred with primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	Primary review 10/29/14 Filing review 10/20/14
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Primary Review (10/29/14)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: 1/23/15 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy(BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done *(Send email to CDER OND IO)*
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

CHRISTINA D MARSHALL
02/09/2015
sBLA 125156/106 Checklist

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/BsUFA Action Date: February 6, 2015

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125156/106
Product(s): Lucentis
Short summary of application: New indication for the (b) (4)

FACILITY INFORMATION

Manufacturing Location: Singapore
Firm Name: Roche Singapore Technical Operations Pte. Ltd.
Address: 10 Tuas Bay Link, 637394
FEI: 3007164129
Short summary of manufacturing activities performed: Drug Substance Manufacturing, Certificate of Analysis Release, and Stability Testing

This site was inspected by IOG from 6/16/2014 – 6/24/2014 and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance manufacturing operations. The TRP profile was updated and is acceptable.

Manufacturing Location: Switzerland

[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: Novartis Pharma AG
Address: Lichtstrasse 35
FEI: 3002807772
Short summary of manufacturing activities performed: Drug Product Release, and Stability Testing

This site was inspected by IOG from 12/2/2013 – 12/5/2013 and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The CTB profile was updated and is acceptable.

OVERALL RECOMMENDATIONS:

There are no pending or ongoing compliance actions that prevent approval of this supplement.

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/s/

CHRISTINA A CAPACCI-DANIEL
01/23/2015

PeRC BPCA/Pediatric Study Plan
Subcommittee Meeting Minutes
December 3, 2014

PeRC Members Attending:
Wiley Chambers
George Greeley
Kevin Krudys
Dionna Green
Ruthanna Davi (b) (4)
Dianne Murphy
Kristiana Brugger
Andrew Mosholder (Did not review Cubicin or (b) (4))
Colleen LoCicero
Julia Pinto (Did not review Cubincin, (b) (4)
Greg Reaman
Hari Cheryl Sachs
Michelle Roth-Cline
Tom Smith (b) (4)
Karen Davis-Bruno
Maura O'Leary (Cubincin and (b) (4) reviews only)
Olivia Ziolkowski
Rosemary Addy
Barbara Buch (Did not review Cubicin)
Peter Starke
(b) (4)

BPCA/Initial Pediatric Study Plan

9:00	NDA	21572	Cubicin Partial Waiver/Daptomycin Amended Written Request	(1) Complicated skin and skin structure infections (cSSSI) (2) Staphylococcus aureus bloodstream infections (bacteremia)
9:10	IND	119939	Ivabradine Written Request	(b) (4)
10:00	IND		(b) (4)	
10:20	IND		(b) (4)	
10:40	IND		(b) (4)	
	IND	(b) (4)		
	IND	*119382*	*Nivolumab iPSP (Full Waiver)*	*Treatment of patients with squamous cell cancers* (b) (4)
	IND			(b) (4)
	IND			(b) (4)

	IND			(b) (4)
	IND	(b) (4)		
	IND	*109763*	*MDX-8704 (memantine hcl/donepezil hcl) Agreed iPSP (Full Waiver)*	*Alzheimer's Disease*
	IND	*106858*	*Dexlansoprazole Agreed iPSP (Partial Waiver)*	*Gastroesophageal Reflux Disease (GERD)*
	IND		(b) (4)	
	IND	*8633*	*Lucentis (ranibizumab) Agreed iPSP (Full Waiver)*	(b) (4)

Cubicin Partial Waiver/Daptomycin Amended Written Request

- Proposed Indication: (1) Complicated skin and skin structure infections (cSSSI) (2) Staphylococcus aureus bloodstream infections (bacteremia)
- The Division clarified that a nonclinical study demonstrated potential irreversible effects on muscular, neuromuscular and nervous system findings in neonatal dogs treated with IV daptomycin. Based on this finding, the division recommends that studies not be performed in patients less than 1year of age, including neonates.
- *PeRC Recommendations*:
    - The PeRC agreed with converting the existing PREA PMR to a partial waiver in patients ages birth to less than one year of age because the product would be unsafe (see discussion above). Labeling will reflect the safety concern.
    - The PeRC agreed to the modifications in the age groups to be studied in the daptomycin Amended Written Request.
    - The PeRC noted that the neonatal dog study was not included in the WR. In the future, nonclinical studies should be included in any WR issued.

Ivabradine Written Request

- Proposed Indication: (b) (4)
- The Division noted that the studies included in the WR have already been completed but not submitted. These studies included were all requested by EMA as part of the product's PIP. The PeRC noted that the first study is a bioequivalence study performed only in healthy adult subjects and such a study should not be included in a WR.
- The Division's recommendations regarding the issuance of this WR were divided. One division representative disagreed that the WR should be issued. This representative stated that the endpoint for study chosen (decrease in HR) is not clearly a clinically meaningful endpoint in children. He also noted that pediatric patients with heart failure due to dilated cardiomyopathy may rely on HR to maintain cardiac output and decreases in HR may worsen heart failure symptoms. However, another division representative noted that in adult patients with dilated cardiomyopathy, reduction in HR appeared to provide benefit, and that the benefit appeared to be more than in patients with heart failure due to ischemic cardiac disease. Some PeRC members also expressed concern about clinical

meaningfulness of the endpoint chosen. However, both the PeRC and the division noted that fully powered studies to evaluate heart failure in pediatric patients based on a clinically meaningful endpoint may be impossible or highly impracticable. After discussions, the PeRC recommended that further review of the WR in its current form should be tabled until additional discussions and communication with the sponsor could be performed.

- *PeRC Recommendations*:
    - Option 1: Send the sponsor an inadequate PPSR letter and include in such a letter, specific concerns and issues to be addressed in a subsequent PPSR. These issues may include the following information:
        - Additional information to support the chosen endpoint (e.g., top line summary data from completed pediatric study that supports the safety and hypothesis that HR reduction may be of benefit)
        - Additional data from adult studies that support the chosen endpoint
        - Consideration of expansion of the current study in order to more fully evaluate the secondary endpoints. The number of patients required to complete such a study would need to be evaluated by statisticians
        - Consideration of a separate study with a different endpoint (e.g., time to rehospitalization)
        - Consideration of co-primary endpoint/composite endpoint to increase confidence in the use of HR as a primary endpoint
    - Option 2: Proceed with a review of the WR as currently submitted (this would need to be rescheduled with the PeRC). The PeRC staff will work with the division to reschedule, if this option is preferred.
    - The PeRC also recommended that the PDCO decision regarding the PIP and the requirement to perform the completed pediatric study be reviewed by the division. OPT will obtain the PDCO decision and forward these documents to the division.
    - The PeRC also recommended that the division consider discussion of this product at a future pediatric cluster call if questions persist after review of the PDCO documents.

(b) (4)

(b) (4)

(b) (4)

Nivolumab iPSP

- Proposed Indication: Treatment of patients with squamous cell cancers (b) (4)
- *PeRC Recommendations*:
  - The PeRC agreed with the plan for full waiver for this product.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

MDX-8704 (memantine hcl/donepezil hcl) Agreed iPSP

- Proposed Indication: Alzheimer's Disease
  - The PeRC agreed with the plan for full waiver for this product.

Dexlansoprazole Agreed iPSP

- Proposed Indication: Gastroesophageal Reflux Disease (GERD)
  - The PeRC agreed with (b) (4) for this product.
  - Some PeRC members questioned the agreed upon timelines for this product, which are lengthy.

(b) (4)

Lucentis Agreed iPSP

- Proposed Indication: (b) (4)
  - The PeRC agreed with the plan for full waiver for this product.

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/s/

GEORGE E GREELEY
12/22/2014

Benton, Sandra J

From: Benton, Sandra J
Sent: Monday, November 24, 2014 1:00 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Marshall, Christina; Lloyd, Rhea; Boyd, William M; Albrecht, Renata; Chambers, Wiley A
Subject: RE: December 1, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 8633

As the Council agrees with DTOP's recommendation to grant Genentech's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the December 1, 2014 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

From: Benton, Sandra J
Sent: Monday, November 17, 2014 1:33 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Marshall, Christina; Lloyd, Rhea; Boyd, William M; Albrecht, Renata; Chambers, Wiley A
Subject: December 1, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 8633

Hi! OMP has scheduled a Medical Policy Council discussion on December 1, 2014 regarding the breakthrough therapy designation request from Genentech for its IND 8633, Lucentis (ranibizumab injection) for the treatment of diabetic retinopathy in patients with diabetic macular edema.

DTOP recommends that this breakthrough therapy request be granted. Attached is DTOP's background on the breakthrough therapy designation with its rationale for granting the request.

DTOP has asked if this request can be reviewed by email.

Would you please review DTOP's recommendation and let me know by COB Monday, November 24 if –

- You agree with DTOP's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DTOP's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DTOP's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for IND 8633.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: Breakthrough Therapy Designation_ ind 8633.doc >> << File: IND 8633 BTDR.PDF >>

PeRC PREA Subcommittee Meeting Minutes
November 5, 2014

PeRC Members Attending:
Robert Nelson (acting as PeRC chair for Lynne Yao)
Rosemary Addy
Jane Inglese
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Peter Starke
Gregory Reaman
Freda Cooner
Lily Mulugeta
Olivia Ziolkowski
Michelle Roth-Cline (for Robert Nelson)
Julia Pinto

Agenda

NDA	206307	Xtoro (finafloxacin) Partial Waiver/Assessment (Written Request -Exclusivity Granted)	Treatment of acute otitis externa
NDA	202813/007	QNASL (beclomethasone) Assessment	Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis
NDA	205122/001	Qudexy XR (topiramate ER) Assessment	Initial monotherapy in patients 2 to 10 years of age with partial onset (POS) or primary generalized tonic-clonic (PGTC) seizures
NDA	(b) (4)	(b) (4)	(b) (4)
BLA	125156/106	Lucentis (ranibizumab) Full Waiver	Treatment of (b) (4)

Xtoro (finafloxacin) Partial Waiver/Assessment (Written Request -Exclusivity Granted)

- NDA 206307 seeks approval for Xtoro (finafloxacin) for treatment of acute otitis externa.
- The application triggers PREA as a new active ingredient.
- The application has a PDUFA a goal date of December 25, 2014.
- *PeRC Recommendations:*
    - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 1 year because studies would be impossible or highly impracticable.
    - The PeRC agreed with the assessment for pediatric patients aged 1 to 17 years.

QNASL (beclomethasone) Assessment

- NDA 202813/007 seeks marketing approval QNASL (beclomethasone) for treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in patients 4 years of age and older.
- The application has a PDUFA a goal date of December 27, 2014.
- *PeRC Recommendations:*
    - The PeRC agreed with the assessment for pediatric patients aged 4 to 11 years.

Qudexy XR (topiramate ER) Assessment

- NDA 205122/001 seeks marketing approval for Qudexy XR (topiramate ER) for initial monotherapy in patients 2 to 10 years of age with partial onset (POS) or primary generalized tonic-clonic (PGTC) seizures.
- The application has a PDUFA a goal date of March 30, 2015.
- *PeRC Recommendations:*
    - The PeRC agreed with the assessment for pediatric patients aged 2 to 10 years.

(b) (4)

(b) (4)

Lucentis (ranibizumab) Full Waiver

- BLA 125156/106 seeks marketing approval for Lucentis (ranibizumab) for treatment of (b) (4).
- The application triggers PREA as a new indication.
- The application has a PDUFA a goal date of February 6, 2015.
- *PeRC Recommendations:*
    - The PeRC agreed with a full waiver because studies would be impossible or highly impracticable.

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/s/

JANE E INGLESE
11/17/2014

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/BsUFA Action Date: February 6, 2015

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125156/106
Product(s): Lucentis
Short summary of application: New indication for the treatment (b) (4)

FACILITY INFORMATION

Manufacturing Location: Singapore
Firm Name: Roche Singapore Technical Operations Pte. Ltd.
Address: 10 Tuas Bay Link, 637394
FEI: 3007164129
Short summary of manufacturing activities performed: Drug Substance Manufacturing, Certificate of Analysis Release, and Stability Testing

Manufacturing Location: Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35
FEI: 300280772
Short summary of manufacturing activities performed: Drug Product Release, and Stability Testing

[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."

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/s/

CHRISTINA D MARSHALL
11/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 8633

ADVICE/INFORMATION REQUEST

Genentech, Inc.
Attention: Clara Cambon, PharmD
Program Management-IVO
1 DNA Way, MS 241B
South San Francisco, CA 94080-4990

Dear Dr. Cambon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lucentis (ranibizumab injection). We also refer to your submission dated and received July 17, 2014, containing your initial Pediatric Study Plan (iPSP) and your submission dated and received October 31, 2014, containing your revised agreed PSP.

We acknowledge your plan to request a full waiver for the study of Lucentis in pediatric patients aged birth to 17 years old for (b) (4) We have completed our review of the submission, and we confirm our agreement to your PSP. We have no further comments on your PSP. A clean copy of the revised agreed PSP is attached for your reference.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

  If your IND is not in eCTD format:

  - you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

  - if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

SUBMISSION REQUIREMENTS

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see
http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, call Christina Marshall, Regulatory Project Manager, at 301-796-3099.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Genentech, Inc. PSP dated October 31, 2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Christina Marshall RPM, Office of Antimicrobial Products Division of Transplant and Ophthalmology 301-796-3099

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
10/28/14		sBLA 125156/106	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Lucentis	Priority	Biologic	12/29/14

NAME OF FIRM:	
Genentech, Inc.	PDUFA Date: February 7, 2015

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission:
\\CDSESUB1\evsprod\BLA125156\125156.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: 10/30/14 @12:30
Wrap-Up Meeting: 1/5/15

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)

	☐ eMAIL ☐ HAND

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/s/

CHRISTINA D MARSHALL
10/28/2014
sBLA 125156/106 OPDP Consult

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

sBLA 125156/106

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Genentech, Inc.
Attention: Clara Cambon, PharmD
Program Management-IVO
1 DNA Way, MS 241B
South San Francisco, CA 94080-4990

Dear Dr. Cambon:

Please refer to your Biologics License Application (BLA) dated and received August 7, 2014, submitted under section 351(a) of the Public Health Service Act for Lucentis (ranibizumab injection).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application will be considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is February 7, 2015.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 16, 2015.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Christina Marshall, Regulatory Project Manager, at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

WILEY A CHAMBERS
10/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125156/S-106

PRIOR APPROVAL SUPPLEMENT - ACKNOWLEDGEMENT

Genentech, Inc.
Attention: Clara Cambon, Pharm. D.
Regulatory Program Management
1 DNA Way, MS 241B
South San Francisco, CA 94080-4990

Dear Dr. Cambon:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 125156/S-106

PRODUCT NAME: Lucentis (ranibizumab) injection

DATE OF SUBMISSION: August 7, 2014

DATE OF RECEIPT: August 7, 2014

This supplemental application proposes revisions of the Lucentis USPI to include a new indication (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 6, 2014 in accordance with 21 CFR 601.2(a).

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, call me, at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Christina Marshall, MS
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTINA D MARSHALL
08/14/2014
sBLA 125156/106-ACK letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125156

MEETING MINUTES

Genentech, Inc.
Attention: Tammy Rose
Regulatory Program Management
1 DNA Way, MS 241B
South San Francisco, CA 94080-4990

Dear Ms. Rose:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Lucentis (ranibizumab injection).

We also refer to the June 26, 2013, meeting between representatives of your firm and the FDA. The purpose of the meeting was to discuss the data to be submitted in order to fulfill the two Postmarketing Commitments described in the approval letter for sBLA 125156/S-076, dated August 10, 2012.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Judit Milstein, Chief Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Minutes of the Meeting
Genentech's preliminary comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	June 26, 2013, 12:00-1:00 PM
Meeting Location:	FDA/White Oak Campus 10903 New Hampshire Avenue Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	sBLA 125156
Product Name:	Lucentis (ranibizumab injection)
Indication:	Treatment of Diabetic Macular Edema (DME)
Sponsor/Applicant Name:	Genentech, Inc.
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Judit R. Milstein

FDA ATTENDEES

Renata Albrecht, Director, Division of Transplant and Ophthalmology Products
Wiley A. Chambers, Deputy Director
William M. Boyd, Clinical Team Leader
Rhea Lloyd, Clinical Reviewer
Lucious Lim, Clinical Reviewer
Martin Nevitt, Clinical Reviewer
Jennifer Harris, Clinical Reviewer
Sonal Wadhwa, Clinical Reviewer
Yan Wang, Biostatistics, Team Leader
Gerlie Gieser, Clinical Pharmacology Reviewer
Philip Colangelo, Clinical Pharmacology Team Leader (on the phone)
Christina Marshall, Regulatory Project Manager
Judit Milstein, Chief, Project Management Staff

SPONSOR ATTENDEES

(b) (6) Product Development Regulatory
Jason S. Ehrlich, Medical Director, Ophthalmology
Zdenka Haskova, Associate Medical Director, Ophthalmology
Dana McClintock, Global Development Team Leader
Tammy Rose, Associate Director, Product Development Regulatory
Roman Rubio, Group Medical Director, Ophthalmology

Jiameng Zhang, Statistical Scientis, Biostatistics
Karen McKeown, Biostatistician II, Biostatistics
Kristina Vlaovic, Global Regulatory Franchise Head Ophthalmology and Respiratory

BACKGROUND
sBLA 125156/S-076, which provides for the treatment of patients with DME was approved on August 10, 2012. At the time of this approval, Genentech committed to the following postmarketing commitments:

1. Evaluate the efficacy of Lucentis in bilateral dosing for the treatment of patients with diabetic macular edema and

2. Evaluate the efficacy of Lucentis for the treatment of diabetic macular edema if treatment is discontinued after at least 1 year of therapy

During discussions held between the Division and Genentech it was noted that these postmarketing commitments might be answered utilizing existing data collected within the FVF4168g and FVF4170g trials and the DRCR.net Protocol 1 trial.

Genentech requested this meeting to discuss their plan for addressing the above mentioned postmarketing commitments.

Preliminary responses to the questions posted in the briefing document dated May 24, 2013, were sent on June 18, 2013. Genentech provided via e-mail a response to these comments and additional clarifying information (see attachment). For the purposes of these minutes, the questions posted by the applicant in the briefing document are in **bold** format, the preliminary responses are in *italics* and the meeting discussions are in normal font.

DISCUSSION
Question 1
Does the Division agree that the data presented adequately evaluate the efficacy of Lucentis in bilateral dosing for the treatment of patients with DME?

Preliminary Comments:
Potentially. The Agency would need to review a supplemental application to make formal determination of the efficacy of Lucentis in bilateral dosing for the treatment of patients with DME. In the submission, please include all measurements of visual acuity and identify them as the time from first injection in the particular eye being measured.

Meeting discussion:

1. The submission to the NDA needs to clearly identify it as a response to Postmarketing Commitment #1.

2. The submission is expected to contain a summary report as well as electronic datasets containing the individual patients' data. The Division clarified that all measurements of visual acuity evaluated during the trials, at all time-points, for all patients, be included in the submission. The Division also requested that Genentech submit the programs used to analyze the datasets in order to reproduce the results presented in the summary report.

3. The Division stated that although the overall summaries and conclusions can be included in one document, the analysis programs and datasets need to be submitted separately for each trial. The Division also recommended not pooling the data of studies FVF4168g and FVF4170g with the data of the DRCR study.

4. The Division stated that if labeling changes are warranted, the information needs to be submitted separately as a supplement.

Question 2
Does the Division agree that the data presented adequately evaluate the efficacy of Lucentis for the treatment of DME, if treatment is discontinued after at least 1 year of therapy?

Preliminary Comments:
No. The Division does not agree that the data presented adequately evaluate the efficacy of Lucentis for the treatment of DME, if treatment is discontinued after at least 1 year of therapy.

The very small number of patients (i.e., reported as approximately 10 patients) who permanently discontinued treatment after 1 year is not sufficient enable reliable conclusions.

Meeting Discussion:

5. Genentech clarified that the submission contained two definitions of "discontinued treatment." The 10 patients mentioned in the Division's response pertain to patients who permanently discontinued monthly therapy and who were further followed in Studies FVF4168g and FVF4170g. The other definition of "discontinued treatment" was 875 patients who received ranibizumab treatment for at least 12 or 36 months in Studies FVF4168g or FVF4170g and at least 12 months in Protocol I. These patients discontinued monthly treatment (FVF4168g/FVF4170g) or near-monthly (Protocol I) ranibizumab treatment and were later evaluated for return of disease activity. Treatment was then given if patients met protocol defined retreatment criteria. The Division agreed that this number of patients should be sufficient to address PMC #2.

6. The submission is expected to contain a summary report as well as datasets.

7. The Division requested that information on the attrition rate be broken down by months (e.g., 3 months, 6 months, 12 months).

8. The Division also recommended including information on those groups that never received further treatment as well as information on follow-up time points after treatment.

9. The Division stated that the DRCR studies may be less relevant to this Postmarketing Commitment. Genentech should submit the DRCR.net data if it will provide additional information relevant to PMC#2.

10. The Division stated that if labeling changes are warranted, the information needs to be submitted separately as a supplement.

Question 3
Does the Division agree that a summary report describing the data presented in the pre-meeting package is sufficient to support the fulfillment of the DME PMCs?

Preliminary Comments:
No. The summary report(s) provided in the Meeting Package dated May 24, 2013, do not contain sufficient detail to allow the Agency to make a determination about the fulfillment of the DME PMCs. It is acceptable to pool the reports for FVF4168g and FVF4170g, but the report for DRCR.net Protocol I should NOT be pooled with FVF4168g and FVF4170g.

In the submission, please include all measurements of visual acuity and identify them as the time from first injection in the particular eye being measured.

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
The Division will issue the minutes of the meeting within 30 days.

ATTACHMENTS AND HANDOUTS
Genentech's responses to the Division's preliminary comments.

Genentech's responses to the Division's preliminary comments

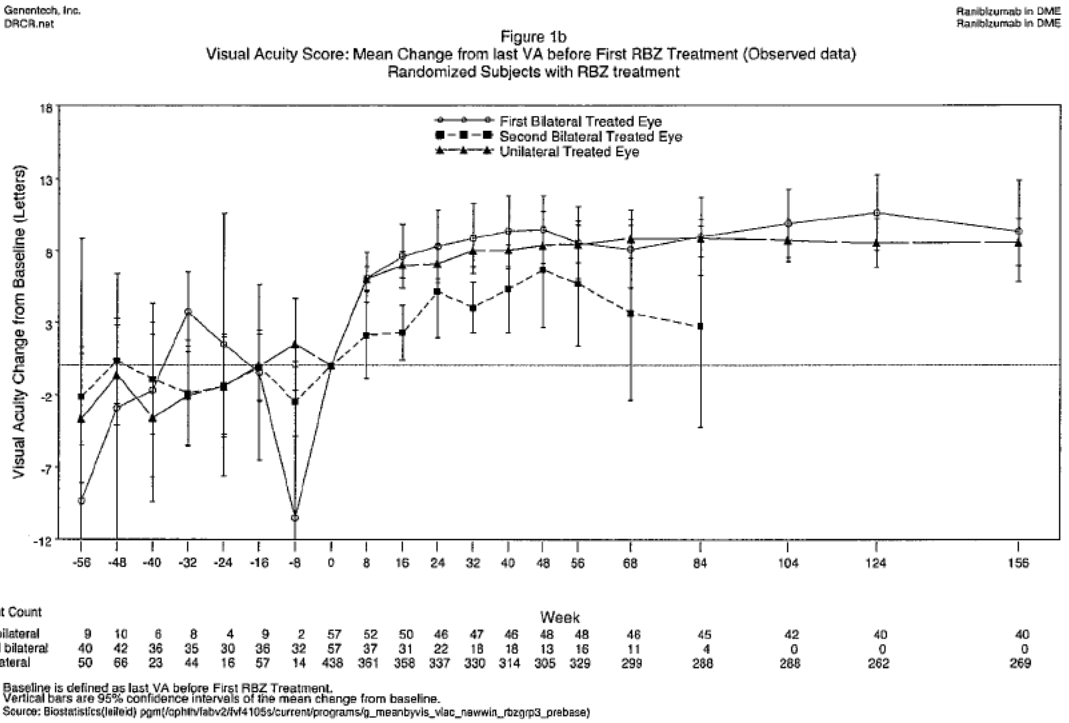
Genentech would like to thank the Division for the preliminary comments received on 18 June 2013 in preparation for our 26 June 2013 guidance meeting to discuss the ranibizumab DME post-marketing commitments. To focus our discussion during the meeting, we have described below additional points where we feel further clarification or discussion is needed.

Genentech Question 1: Does the Division agree that the data presented adequately evaluate the efficacy of Lucentis in bilateral dosing for the treatment of patients with DME?

DTOP Preliminary Comments received 18 June:
Potentially. The Agency would need to review a supplemental application to make formal determination of the efficacy of Lucentis in bilateral dosing for the treatment of patients with DME. In the submission, please include all measurements of visual acuity and identify them as the time from first injection in the particular eye being measured.

Genentech Response:
Genentech would like to clarify the meaning of "all measurements of visual acuity."

Genentech interprets the Division's request to indicate that the data previously provided within the pre-meeting package should also include the mean BCVA at every available time point before the first ranibizumab injection for each eye. An example of the data represented in this way is provided in the figure below, in which available data for mean BCVA *before* the first ranibizumab injection for each group (first bilaterally treated eye, second bilaterally treated eye, and unilaterally treated eye) is also plotted for DRCR.net Protocol I data. Please note that data before the first ranibizumab injection for the first bilaterally treated eye are very limited. Similar graphs could be generated for FVF4168g and FVF4170g data.



<u>Genentech Question 2:</u> Does the Division agree that the data presented adequately evaluate the efficacy of Lucentis for the treatment of DME, if treatment is discontinued after at least 1 year of therapy?

<u>DTOP Preliminary Comments received 18 June:</u>

No. The Division does not agree that the data presented adequately evaluate the efficacy of Lucentis for the treatment of DME, if treatment is discontinued after at least 1 year of therapy. The very small number of patients (i.e., reported as approximately 10 patients) who permanently discontinued treatment after 1 year is not sufficient enable reliable conclusions.

<u>Genentech Response</u>:

In the meeting on 26 June, Genentech would like to clarify the Division's definition of "discontinued treatment" and additionally discuss the objectives of this PMC question.

In the pre-meeting package, Genentech provided data derived from two potential definitions of treatment discontinuation: 1) discontinuation from monthly or near-monthly therapy to less intensive therapy as needed (larger data set available), and 2) permanent discontinuation from monthly therapy (small data set available).

For the first potential definition, in the pre-meeting package, we described an analysis of over 800 patients who received ranibizumab treatment for at least 12 or 36 months in Studies FVF4168g and FVF4170g and at least 12 months in Protocol I. These patients (N=875) discontinued monthly (FVF4168g/FVF4170g) or near-monthly (Protocol I) ranibizumab treatment and were then evaluated for return of disease activity. Treatment was given if patients met retreatment criteria defined in the protocols; for example, in the open-label extension of

Studies FVF4168g/FVF4170g, retreatment was called for when a patient experienced loss of ≥ 5 letters BCVA from the Month 36 baseline and/or the return of macular edema based on OCT assessment. These criteria were set forth in order to maintain patients' visual acuity within 1 line of their outcome at Month 36.

On average, in this analysis, retreatment was performed by 4-5 months after Month 36 in FVF4168g and FVF4170g and by 10-14 months after Month 12 in DRCR.net Protocol I. Sixty-six to seventy percent (66-70%) of patients received retreatment by 6 months after discontinuation of monthly treatment in FVF4168g and FVF4170g; forty-four to fifty-eight percent (44-58%) of patients received retreatment by 6 months after 1 year of ranibizumab treatment in DRCR.net Protocol I. The average loss in BCVA prior to retreatment was 2-4 letters for FVF4168g and FVF4170g and 1-2 letters for DRCR.net Protocol I. The average increase in CFT prior to retreatment was 14-23 μm for FVF4168g and FVF4170g and 9-20 μm for DRCR.net Protocol I. These data suggest that there were trends of VA loss (within one line) and recurrence of edema after discontinuation of at least one year of monthly or nearly monthly therapy (and before retreatment). The majority of patients required additional treatment on an as needed basis to maintain the visual benefit they achieved after at least one year of monthly or near monthly treatment with ranibizumab. In addition, we conclude that VA benefit is well maintained when less intensive (i.e. as needed) therapy is instituted in patients after at least one year of a more intensive treatment regimen.

These results were consistent with the findings from the second potential definition of treatment discontinuation, i.e. from the small group of patients who had permanently discontinued therapy (n=13) and who were further followed in Studies FVF4168g and FVF4170g. For this small group of patients, vision also appeared to be relatively stable for approximately 6 months after permanent discontinuation of therapy.

Genentech believes these data are representative of real world use and representative of the likely visual outcomes expected once treatment with ranibizumab is discontinued. Furthermore, Genentech believes these data support and answer the post-marketing question of what occurs when VEGF is no longer inhibited in DME patients who have received chronic anti-VEGF therapy. Importantly, it should be noted that in the teleconference held on 07 August 2012 regarding the DME post-marketing commitments, Genentech and the Division discussed the design of the open-label extension phase of Studies FVF4168g and FVF4170g and the potential for these patients to be included in an analysis to answer the post-marketing question around treatment discontinuation after at least 1 year of therapy.

Thus, in the meeting on 26 June, Genentech would like to better understand the Division's definition of "treatment discontinuation" and the limitations of the proposed data to fulfill this post-marketing commitment.

Genentech Question 3: Does the Division agree that a summary report describing the data presented in the pre-meeting package is sufficient to support the fulfillment of the DME PMCs?

DTOP Preliminary Comments Received 18 June:

No. The summary report(s) provided in the Meeting Package dated May 24, 2013, do not contain sufficient detail to allow the Agency to make a determination about the fulfillment of the DME PMCs. It is acceptable to pool the reports for FVF4168g and FVF4170g, but the report for DRCR.net Protocol I should NOT be pooled with FVF4168g and FVF4170g.

In the submission, please include all measurements of visual acuity and identify them as the time from first injection in the particular eye being measured.

Genentech Response:
Genentech would like to further understand the Division's preferred structure for submission of the data to fulfill the post-marketing commitment in the setting where a supplemental application (sBLA) to revise the Lucentis USPI was not pursued.

As noted in Question 1, Genentech proposes to supplement the data provided within the pre-meeting package with the additional VA measurements requested by the Division once further clarification is obtained on the meaning of "all measurements of visual acuity." Within the analyses, Genentech agrees that data from the FVF4168g and FVF4170g studies will not be pooled with the DRCR.net Protocol I trial. We believe that a single report (containing the separate analyses from DRCR.net Protocol I and pooled Studies FVF4168g/FVF4170g) would be appropriate, so that shared background, common findings, and conclusions from the totality of the data could be discussed in a single report without repetition

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/s/

WILEY A CHAMBERS
07/17/2013