

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125156Orig1s114

Trade Name: LUCENTIS

Generic or Proper Name: ranibizumab

Sponsor: Genentech, Inc.

Approval Date: April 15, 2017

Indication:

LUCENTIS, 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)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



BLA 125156/S-114

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Katherine Valentine
Regulatory Program Management
1 DNA Way, MS 35-5F
South San Francisco, CA 94080

Dear Ms. Valentine:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received October 18, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lucentis (ranibizumab injection).

This Prior Approval supplemental biologics application proposes the additional indication of treatment of diabetic retinopathy.

APPROVAL & LABELING

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.

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 text for the prescribing information, 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 include 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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125156.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application since studies are impossible or highly impracticable because diabetic retinopathy rarely occurs in the pediatric population.

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 prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, 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 Lois Almoza, M.S., Regulatory Project Manager, at (301) 796-1600.

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

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

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
04/15/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

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) for intravitreal injection For Intravitreal Injection Initial U.S. Approval: 2006

-----RECENT MAJOR CHANGES-----	
Indications and Usage, Diabetic Retinopathy (1.4)	04/2017
Indications and Usage, Myopic Choroidal Neovascularization (1.5)	01/2017
Dosage and Administration (2)	04/2017
Dosage Forms and Strengths (3)	04/2017

-----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 (DR) (1.4)
- Myopic Choroidal Neovascularization (mCNV) (1.5)

-----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) (2.4): LUCENTIS 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

• Myopic Choroidal Neovascularization (mCNV) (2.5): LUCENTIS 0.5 mg (0.05 mL) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months. Patients may be retreated if needed.

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

- Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections:
 - 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
- 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: 04/2017

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- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)
- 1.4 Diabetic Retinopathy (DR)
- 1.5 Myopic Choroidal Neovascularization (mCNV)

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- 2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
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* 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 (DR)
- 1.5 Myopic Choroidal Neovascularization (mCNV)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION .

Vials: A 5-micron sterile filter needle (19-gauge x 1-1/2 inch), a 1-mL Luer lock syringe and a 30-gauge x 1/2 inch sterile injection needle are needed but not included.

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

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL 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 9 months after three 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 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) and Diabetic Retinopathy (DR)

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

2.5 Myopic Choroidal Neovascularization (mCNV)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to 3 months. Patients may be retreated if needed [(see *Clinical Studies 14.5*)].

2.6 Preparation for Administration

Prefilled Syringe:

The prefilled syringe is sterile and is for single use only. **Do not** use the product if the packaging is damaged or has been tampered with.

To prepare LUCENTIS for intravitreal administration, please adhere to these instructions for use. Read all the instructions carefully before using the prefilled syringe.

The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.

For the intravitreal injection, a 30-gauge x ½ inch sterile injection needle should be used (not provided).

Note: the dose must be set to 0.05 mL.

Device description

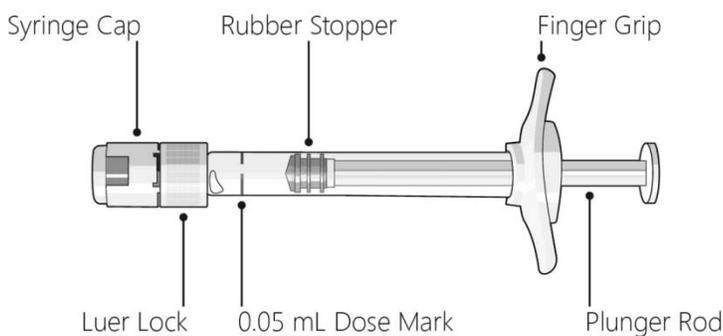


Figure 1

Step 1: Prepare

- Make sure that your pack contains a sterile prefilled syringe in a sealed tray.
- Peel the lid off the syringe tray and, using aseptic technique, remove the syringe.

Step 2: Inspect syringe

- LUCENTIS should be colorless to pale yellow.
- **Do not** use the prefilled syringe if:
 - the syringe cap is detached from the Luer lock.
 - the syringe is damaged.
 - particulates, cloudiness, or discoloration are visible.

Step 3: Remove syringe cap

- Snap off (**do not** turn or twist) the syringe cap (see Figure 2).

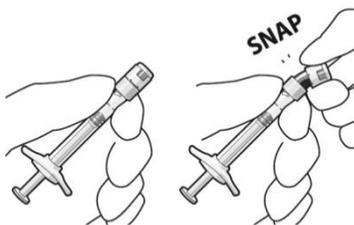


Figure 2

Step 4: Attach needle

- Attach a 30G x ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock (see Figure 3).
- Carefully remove the needle cap by pulling it straight off.

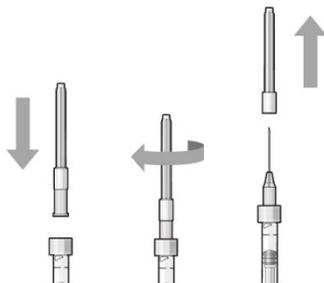


Figure 3

Note: Do not wipe the needle at any time.

Step 5: Dislodge air bubbles

- Hold the syringe with the needle pointing up.
- If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).

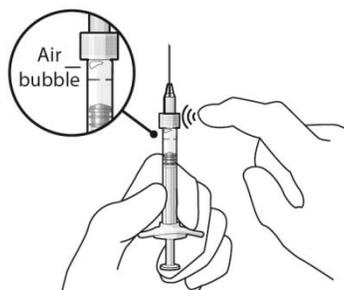


Figure 4

Step 6: Expel air and adjust drug dose

Hold the syringe at eye level, and carefully push the plunger rod until the **edge below the dome** of the rubber stopper is aligned with the 0.05 mL dose mark (see Figure 5).

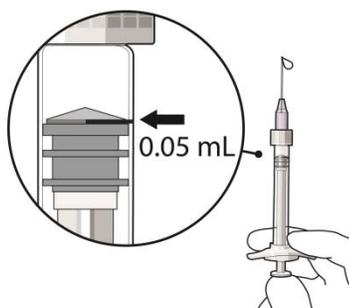


Figure 5

Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.

Step 7: Inject

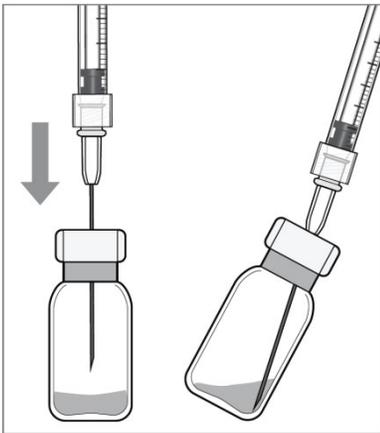
- The injection procedure should be carried out under aseptic conditions.
- Insert the needle into the injection site.
- Inject slowly until rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL.
- After injection, **do not** recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

Vial:

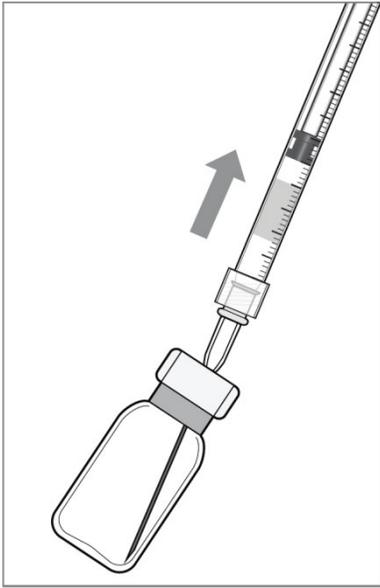
Using aseptic technique, all of the LUCENTIS vial contents are withdrawn through a 5-micron (19-gauge x 1-1/2 inch), sterile filter needle attached to a 1 mL syringe (not included). The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge x 1/2 inch needle for the intravitreal injection.

Use aseptic technique to carry out the following preparation steps:

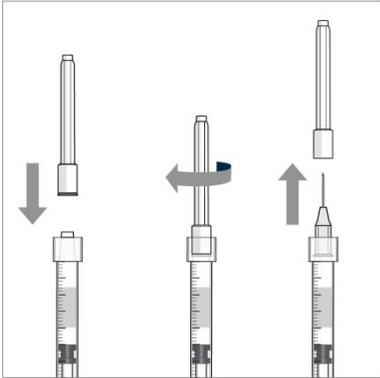
1. Prepare for intravitreal injection with the following medical devices for single use (not included):
 - a 5-micron sterile filter needle (19-gauge x 1-1/2 inch)
 - a 1 mL sterile Luer lock syringe (with marking to measure 0.05 mL)
 - a sterile injection needle (30-gauge x 1/2-inch)
2. Before withdrawal, disinfect the outer part of the rubber stopper of the vial.
3. Place a 5-micron filter needle (19-gauge x 1-1/2 inch) onto a 1 mL Luer lock syringe using aseptic technique.
4. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
5. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.



6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.



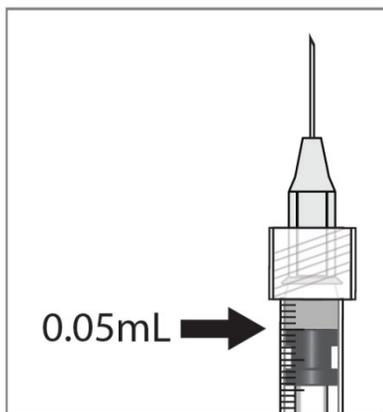
7. The filter needle should be discarded after withdrawal of the vial contents and must not be used for the intravitreal injection.
8. Attach a 30-gauge x 1/2-inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.



9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



10. Hold the syringe at eye level, and carefully push the plunger rod 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 prefilled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new prefilled syringe or vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle (vial only), 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 prefilled syringe designed to provide 0.05 mL for intravitreal injection.

- Colorless to pale yellow 10 mg/mL solution (LUCENTIS 0.5 mg)

Single-use glass vial designed to provide 0.05 mL for intravitreal injection.

- Colorless to pale yellow 10 mg/mL solution (LUCENTIS 0.5 mg)
- Colorless to pale yellow 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. Arterial thromboembolic events 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 (PDT)], 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 Diabetic Macular Edema and Diabetic Retinopathy 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 other sections of the label:

- Endophthalmitis and Retinal Detachments [*see Warnings and Precautions (5.1)*]
- Increases in Intraocular Pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic Events [*see Warnings and Precautions (5.3)*]
- Fatal Events in patients with DME and DR at baseline [*see Warnings and Precautions (5.4)*]

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; in 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 224 patients with mCNV, as well as Studies AMD-4 and D-3, 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	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
	n=250	n=250	n=379	n=379	n=440	n=441	n=259	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 $\geq 5\%$ in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a $\geq 1\%$ 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 reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the 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 PDT. Twelve of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (\pm 2 days) after PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab [*see Clinical Pharmacology (12.1)*], treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data

Animal Data

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.

8.2 Lactation

Risk Summary

There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

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.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential

Infertility

No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

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 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) 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 prefilled syringe or a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use container designed to deliver 0.05 mL of 10 mg/mL LUCENTIS (0.5 mg dose prefilled syringe or 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, 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, mCNV, DR, DME and macular edema following RVO. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

12.2 Pharmacodynamics

Increased 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, mCNV, macular edema following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD and mCNV. 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

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)*].

Myopic Choroidal Neovascularization

On average CFT reductions were observed as early as Month 1, and were greater in the LUCENTIS groups compared to PDT [see *Clinical Studies (14.5)*].

12.3 Pharmacokinetics

In patients with neovascular AMD, following monthly intravitreal administration of 0.5 mg LUCENTIS, mean (\pm SD) maximum ranibizumab serum concentrations were 1.7 (\pm 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

Animal studies have not been conducted to determine the carcinogenic potential of ranibizumab. Based on the anti-VEGF mechanism of action of ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity [see *Females and Males of Reproductive Potential (8.3)*].

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 PDT. Sham PDT (or active PDT) was given with the initial LUCENTIS (or sham) intravitreal injection and every 3 months thereafter if FA 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)

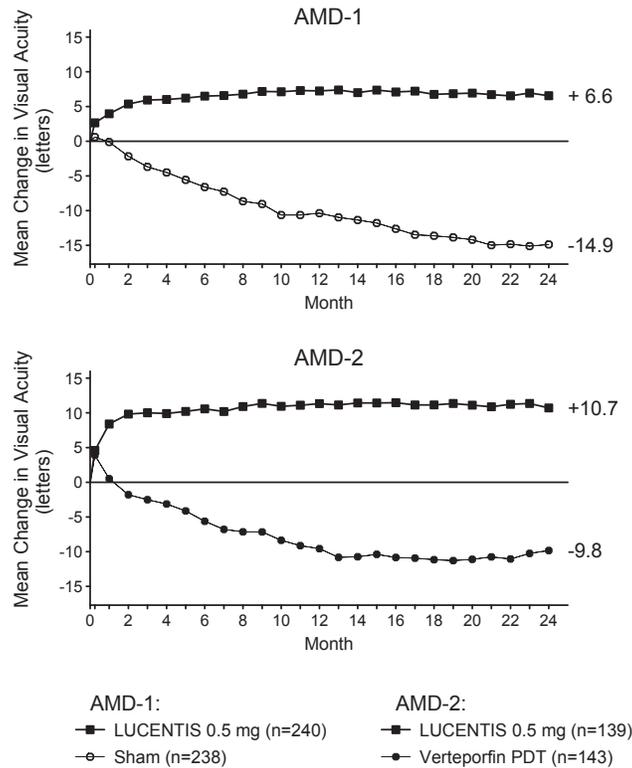
^aAdjusted estimate based on the stratified model; p < 0.01

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

Outcome Measure	Month	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)

^aAdjusted estimate based on the stratified model; p < 0.01

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



^aVisual 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.

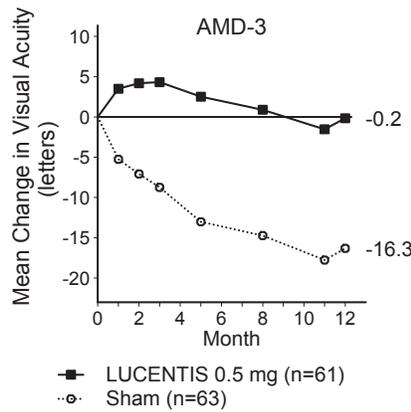
Study AMD-3

Study AMD-3 was a randomized, double-masked, sham-controlled, 2-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 three 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 six total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was the 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 three 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

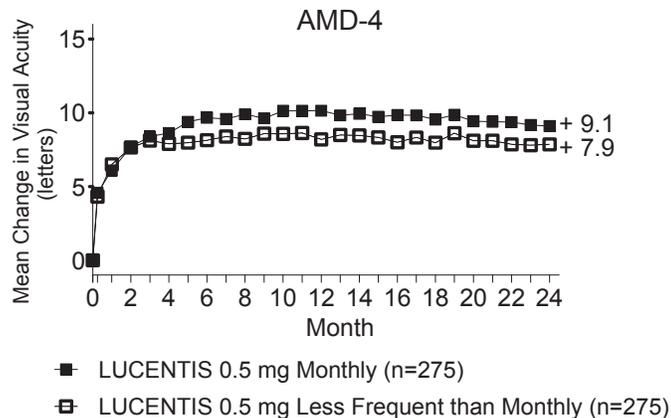
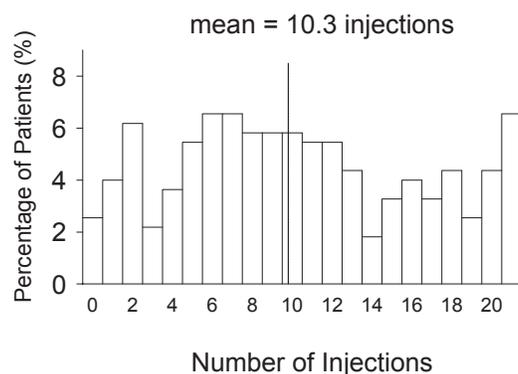


Figure 4

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:

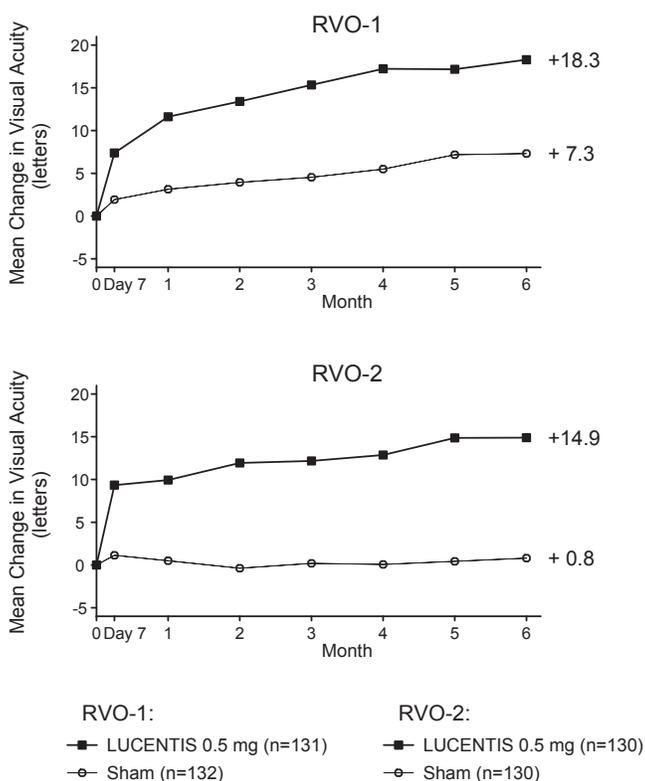
Table 5
Visual Acuity Outcomes at Month 6 in Study RVO-1 and Study RVO-2

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 (DME)

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

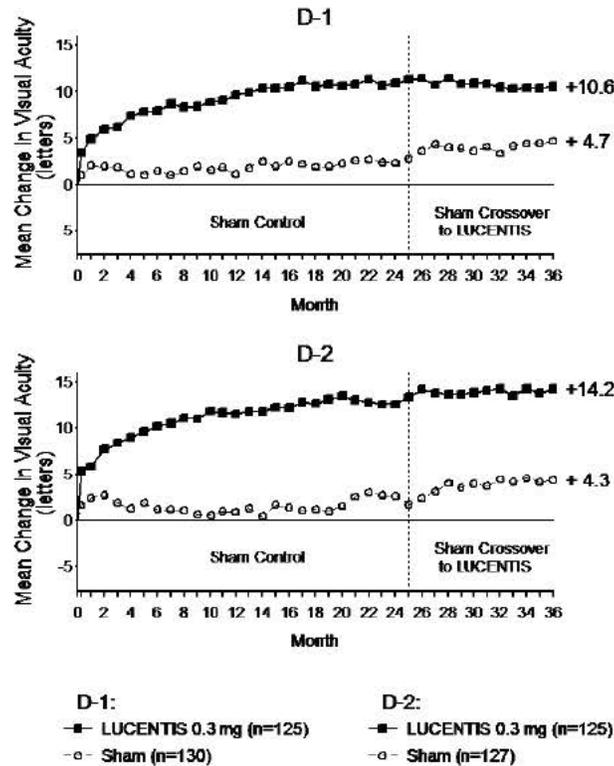
Outcome Measure	Study ^a	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI) ^b
Gain of ≥15 letters in visual acuity (%)	D-1	12%	34%	21% (11%, 30%)
	D-2	18%	45%	24% (14%, 35%)
Loss of <15 letters in visual acuity (%)	D-1	92%	98%	7% (2%, 13%)
	D-2	90%	98%	8% (2%, 14%)
Mean change in visual acuity (letters)	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 ≤ 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

Visual acuity 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 (DR)

Efficacy and safety data of LUCENTIS are derived from Studies D-1 and D-2 [see *Clinical Studies (14.3)*] and D-3. All enrolled patients in Studies D-1 and D-2 had DR and DME at baseline. Study D-3 enrolled DR patients both with and without DME at baseline.

Of the 759 patients enrolled in Studies D-1 and D-2, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scores (ETDRS-DRSS) ranging from 10 to 75. At baseline, 62% of patients had non-proliferative diabetic retinopathy (NPDR) (ETDRS-DRSS less than 60) and 31% had proliferative diabetic retinopathy (PDR) (ETDRS-DRSS greater than or equal to 60). The ETDRS-DRSS 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

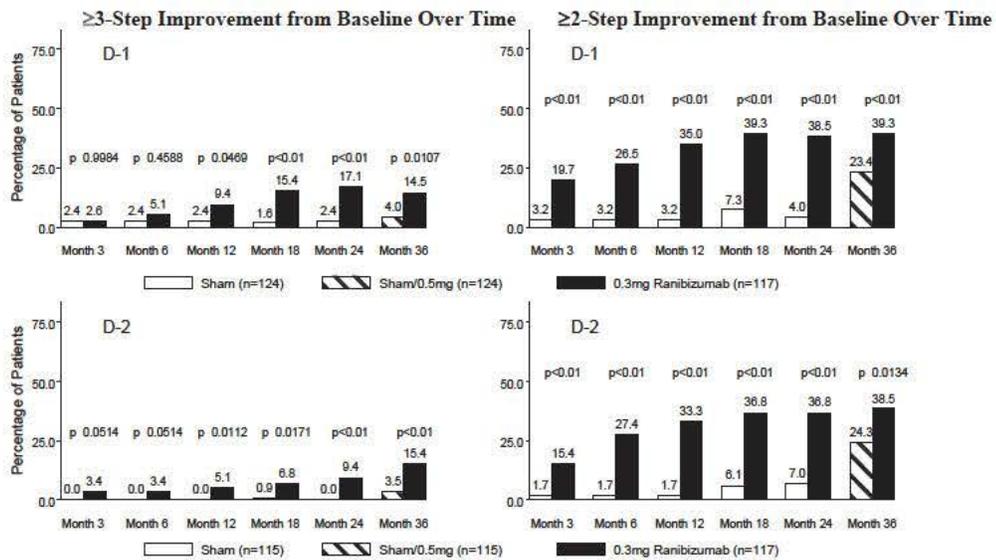
^c $p < 0.05$ for all time points comparing LUCENTIS 0.3 mg to sham from Month 12 through Month 24

^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-DRSS 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-DRSS 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



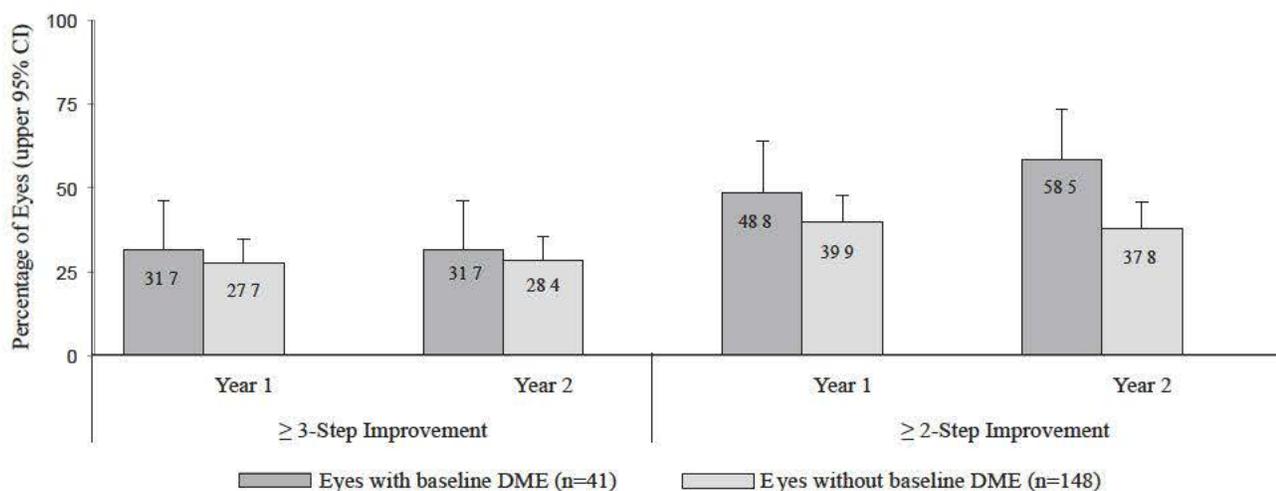
Study D-3 enrolled DR patients with and without DME; 88 (22%) eyes with baseline DME and 306 (78%) eyes without baseline DME and balanced across treatment groups. Study D-3 was a randomized, active-controlled study where patient age ranged from 20 to 83 with a mean age of 51 years. A total of 394 study eyes from 305 patients, including 89 who had both eyes randomized, were enrolled (LUCENTIS, 191 study eyes; pan-retinal photocoagulation; 203 study eyes). All eyes in the LUCENTIS group received a baseline 0.5 mg intravitreal injection followed by 3 monthly intravitreal injections, after which treatment was guided by pre-specified re-treatment criteria. Patients had baseline ETDRS-DRSS ranging from 20 to 85. At baseline, 11% of eyes had NPDR (ETDRS-DRSS less than 60), 50% had mild-to-moderate PDR (ETDRS-DRSS equal to 60, 61, or 65), and 37% had high-risk PDR (ETDRS-DRSS greater than or equal to 71).

An analysis of data from Study D-3 demonstrated that at Year 2 in the LUCENTIS group, 31.7% and 28.4% of eyes in the subgroups with baseline DME and without baseline DME, respectively, had ≥ 3 -step improvement from baseline in ETDRS-DRSS.

Table 8
 Proportion of Eyes with ≥ 3 -Step and ≥ 2 -Step Improvement from Baseline in ETDRS-DRSS at Year 2 in Study D-3

LUCENTIS group		
Outcome Measure (in ETDRS-DRSS)	Eyes with Baseline DME n = 41	Eyes without Baseline DME n = 148
≥ 3 -step improvement from baseline 95% CI for percentage	13 (31.7%) (17.5%, 46.0%)	42 (28.4%) (21.1%, 35.6%)
≥ 2 -step improvement from baseline 95% CI for percentage	24 (58.5%) (43.5%, 73.6%)	56 (37.8%) (30.0%, 45.7%)

Figure 8
Proportion of Eyes in the LUCENTIS group with ≥ 3 -Step and ≥ 2 -Step Improvement from Baseline in ETDRS-DRSS at Year 1 and Year 2 in Study D-3



14.5 Myopic Choroidal Neovascularization (mCNV)

The efficacy and safety data of LUCENTIS were assessed in a randomized, double-masked, active-controlled 3-month study in patients with mCNV. Patients age ranged from 18 to 87 years, with a mean age of 55 years. A total of 276 patients (222 patients in the LUCENTIS treated Groups I and II; 55 patients in the active control PDT group) were enrolled. Patients randomized to the LUCENTIS groups received injections guided by pre-specified re-treatment criteria. The retreatment criteria in Group I were vision stability guided, with the Best Corrected Visual Acuity (BCVA) at the current visit being assessed for changes compared with the two preceding monthly BCVA values. The retreatment criteria in Group II were disease activity guided, based on BCVA decrease from the previous visit that was attributable to intra- or sub-retinal fluid or active leakage secondary to mCNV as assessed by OCT and/or FA compared to the previous monthly visit.

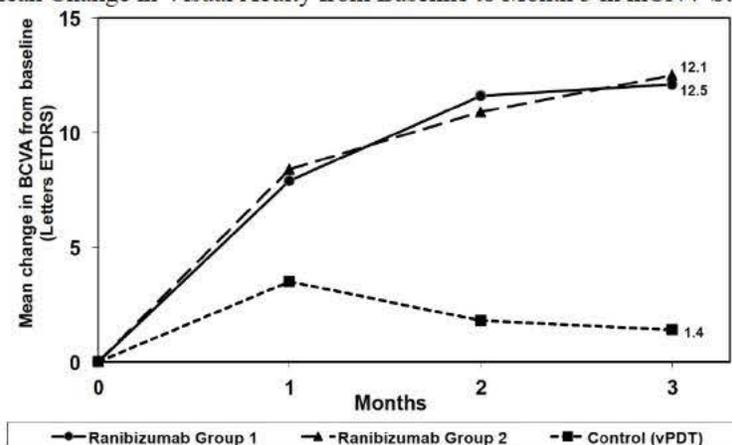
Visual gains for the two LUCENTIS 0.5 mg treatment arms were superior to the active control arm. The mean change in BCVA from baseline at Month 3 was: +12.1 letters for Group I, +12.5 letters for Group II and +1.4 letters for the PDT group. (Figure 9; Table 9). Efficacy was comparable between Group I and Group II.

Table 9
Mean Change in Visual Acuity and Proportion of Patients who Gained ≥ 15 letters from Baseline at Month 3

Study Arms	Mean change in BCVA from baseline (Letters)		Proportion of patients who gained ≥ 15 letters from baseline	
	Mean (SD)	Estimated Difference (95% CI) ^a	Percent	Estimated Difference (95% CI) ^a
Group I	12.1 (10.2)	10.9 (7.6, 14.3)	37.1	22.6 (9.5, 35.7)
Group II	12.5 (8.8)	11.4 (8.3, 14.5)	40.5	26.0 (13.1, 38.9)
Control (PDT)	1.4 (12.2)		14.5	

^a Adjusted estimates based on stratified models; $p < 0.01$

Figure 9
Mean Change in Visual Acuity from Baseline to Month 3 in mCNV Study



The proportion of patients who gained ≥ 15 letters (ETDRS) by Month 3 was 37.1% and 40.5% for LUCENTIS Groups I and II, respectively and 14.5% for the PDT group. The mean number of injections between baseline and Month 3 was 2.5 and 1.8 for Groups I and II, respectively. 41% of patients received 1, 2 or 3 injections between baseline and Month 3 with no injections afterwards.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution. The prefilled syringe has a non-retractable plunger stopper and a syringe cap consisting of a tamper-evident rigid seal with a rubber tip cap including a Luer lock adapter. The prefilled syringe has a plunger rod and a CLEAR finger grip. The prefilled syringe is sterile and is packed in a sealed tray.
- Each LUCENTIS 0.5 mg carton (NDC 50242-080-02) contains a single-use, 2-mL glass vial with a BLUE CAP designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution.
- Each LUCENTIS 0.3 mg carton (NDC 50242-082-02) contains a single-use, 2-mL glass vial with a WHITE CAP designed to deliver 0.05 mL of 6 mg/mL ranibizumab solution.

EACH CARTON IS 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. Protect LUCENTIS prefilled syringe and vials from light and store in the original carton until time of use. Do not open LUCENTIS prefilled syringe sealed tray 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. ©2017 Genentech, Inc.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	April 15, 2017
From	Wiley A. Chambers, MD
BLA #	125156
Applicant	Genentech, Inc.
Date of Submission	October 18, 2016
Type of Application	Supplement 114
Name	Lucentis (ranibizumab injection)
Dosage forms / Strength	Solution for intravitreal injection
Proposed New Indication(s)	For the treatment of diabetic retinopathy
Action:	Approval

1. Introduction

Lucentis (ranibizumab injection) is currently approved for the treatment of diabetic retinopathy in patients with diabetic macular edema. In this supplemental BLA, Genentech seeks to update the Lucentis labeling to expand the indication to include patients with diabetic retinopathy regardless of whether or not they have concurrent diabetic macular edema.

The applicant has submitted the results of Protocol S which was designed to determine the relative efficacy of ranibizumab 0.5 mg injection vs. panretinal photocoagulation (PRP) for improvement in vision of patients with diabetic retinopathy. This study included a mixture of subjects with and without DME. Randomized subjects were stratified based on DME status at baseline.

The Jaeb Center for Health Research (JCHR) was the sponsor of Protocol S and the coordinating center for the Diabetic Research Clinical Research Network (DRCR.net). The JCHR conducted the study, and the DRCR.net supported the identification, design, and implementation of the Protocol S study. This collaboration is referred to as JCHR (DRCR.net).

Genentech did have an opportunity to review JCHR (DRCR.net)'s protocol and provide comments. However, JCHR (DRCR.net) was under no obligation to incorporate those suggestions. Genentech was not involved in the conduct of the study but did provide ranibizumab and funds to the JCHR to defray the study's costs.

2. Background

BLA 125156 for Lucentis (ranibizumab injection), 0.5 mg was approved on June 30, 2006, for the treatment of patients with neovascular (wet) age-related macular degeneration. Subsequently, the following supplemental applications have been approved:

- S-053, for Lucentis (ranibizumab injection), 0.5 mg approved on June 22, 2010, for the treatment of patients with macular edema following retinal vein occlusion.
- S-076, for Lucentis (ranibizumab injection), 0.3 mg approved on August 10, 2012, for the treatment of patients with diabetic macular edema.
- S-106, for Lucentis (ranibizumab injection), 0.3 mg approved on February 6, 2015, for the treatment of diabetic retinopathy in patients with diabetic macular edema.
- S-111, for Lucentis (ranibizumab injection), 0.5 mg approved on January 5, 2017, for the treatment of myopic choroidal neovascularization.

3. CMC

There were no changes in the manufacturing of the drug product. The Office of Biotechnology, Division of Monoclonal Antibodies finalized a review memorandum on March 19, 2017. There are no CMC-related approvability issues. Commercial Lucentis was used in the Protocol S study. The applicant has claimed a categorical exemption from the environmental assessment, which was found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The dosing regimen is the same as previously approved. No new nonclinical studies were submitted with this supplemental BLA. There were no new concerns from the nonclinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

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

6. Clinical/Statistical - Efficacy

Study	Design (Sites)	Population	No. of Subjects Enrolled	Treatment Frequency and Duration
Protocol S (Protocol ML27976)	Multicenter, randomized, single-masked, active treatment-controlled USA	Adult patients with proliferative diabetic retinopathy	305 subjects (394 eyes) RBZ group (n=191 eyes) PRP group (n=203 eyes)	RBZ group: 0.5 mg IVT injection at randomization/baseline, 4-, 8-, and 12-week follow-up visits. Beginning at 16-week visit, eyes were evaluated for retreatment based on appearance of neovascularization. PRP group: A full session of 1200-1600 burns using 500 micron burns on the retina or the equivalent area treated when using indirect laser delivery systems was completed within 56 days of randomization. Study eyes in the PRP group could receive supplemental PRP if neovascularization worsened during the study following completion of the initial PRP session. Eyes in both groups could receive ranibizumab as needed for DME, at baseline or if DME developed during the course of the study.

Efficacy Evaluation

The original primary efficacy variable was the mean change in visual acuity at 2 years from baseline.

Mean Change in Best Corrected Visual Acuity (ETDRS letters) from Baseline in the Study Eye at 2 Years (LOCF) Randomized Eyes

	Ranibizumab 0.5 mg N=191	PRP Total N=203
Baseline		
N	191	203
Mean (SD)	75.0 (12.8)	75.2 (12.5)
Median	77.0	78.0
Min – Max	0.0- 12.0	-4.0 – 7.0
Week 104 (2 Years)		
N	191	203
Mean (SD)	2.7 (17.8)	-0.7 (15.5)
Median (SE)	5.0 (1.3)	1.0 (1.1)
95% CI for mean	(0.2, 5.2)	(-2.8, 1.5)
Difference in means		3.4
95% CI for difference		(0.1, 6.6)
Test for Treatment Difference		
Student t-test (unstratified)		0.0460
ANOVA t-test (stratified)		0.0382

Source: Module 5.3.5.1 CSR ML27976 Section 5.2.1 Table 16

Stratification variables in stratified analyses: baseline DME status and number of eyes enrolled. All CIs are 2-sided. CIs for means and differences in means are based on Student t-distribution (Unstratified). Estimates and CIs for LS means and differences in LS means are from the ANOVA model (stratified).

For this supplemental BLA submission for the treatment of diabetic retinopathy independent of baseline DME studies, the redefined main efficacy measure is: the proportion of eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 2 years.

Proportion of Eyes with ≥ 3 -Step Improvement from Baseline in Ranibizumab Group in ETDRS-DRSS by Baseline DME Status (Eyes with a Valid ETDRS-DRSS at Baseline)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
AT 1 YEAR		
Observed		
N	33	122
n (%)	13 (39.4%)	41 (33.6%)
95% CI for percentage	(22.7%, 56.1%)	(25.2%, 42.0%)
Difference in percentages		5.8%
95% CI for difference		(-12.9%, 24.4%)
Multiple Imputation		
N	41	148
n (%)	16 (40.6%)	54 (36.8%)
95% CI for percentage	(23.8%, 57.4%)	(28.4%, 45.1%)
Difference in percentages		3.9%
95% CI for difference		(-15.3%, 23.0%)
AT 2 YEARS		
Observed		
N	27	116
n (%)	10 (37.0%)	38 (32.8%)
95% CI for percentage	(18.8%, 55.3%)	(24.2%, 41.3%)
Difference in percentages		4.3%
95% CI for difference		(-15.8%, 24.4%)
Multiple Imputation		
N	41	148
n (%)	16 (40.2%)	51 (35.1%)
95% CI for percentage	(22.9%, 57.6%)	(26.9%, 43.4%)
Difference in percentages		5.1%
95% CI for difference		(-13.8%, 24.0%)

Source: Module 2.7.3 SCE Table 9 and 10; Response to IR #4 dated March 24, 2017.

Note: ICs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputation, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 3 -step improvement.

Proportion of Eyes with ≥ 2 -Step Improvement from Baseline in Ranibizumab Group in ETDRS-DRSS by Baseline DME Status (Eyes with a Valid ETDRS-DRSS at Baseline)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
AT 1 YEAR		
Observed		
N	33	122
n (%)	20 (60.6%)	59 (48.4%)
95% CI for percentage	(43.9%, 77.3%)	(39.5%, 57.2%)
Difference in percentages		12.2%
95% CI for difference		(-6.6%, 31.1%)
Multiple Imputation		
N	41	148
n (%)	25 (61.1%)	76 (51.7%)
95% CI for percentage	(44.7%, 77.5%)	(43.2%, 60.2%)
Difference in percentages		9.4%
95% CI for difference		(-9.0%, 27.8%)
AT 2 YEARS		
Observed		
N	27	116
n (%)	18 (66.7%)	49 (42.2%)
95% CI for percentage	(48.9%, 84.4%)	(33.3%, 51.2%)
Difference in percentages		24.4%
95% CI for difference		(4.5%, 44.3%)
Multiple Imputation		
N	41	148
n (%)	27 (66.3%)	68 (46.2%)
95% CI for percentage	(49.4%, 83.3%)	(37.5%, 54.9%)
Difference in percentages		20.1%
95% CI for difference		(0.6%, 39.6%)

Source: Module 2.7.3 SCE Table 9 and 10; Response to IR #4 dated March 24, 2017.

Note: ICs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputations, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 3 -step improvement.

Efficacy Summary:

Eyes in the ranibizumab group experienced improvements of ≥ 3 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

At 2 years in Protocol S, the 0.5 mg ranibizumab PRN treatment group differences for patients without DME compared to those with DME was approximately 21% for the proportion of patients who experienced a ≥ 2 -step improvement from baseline in ETDRS-DRSS and approximately 5% in the for the proportion of patients who experienced a ≥ 3 -step improvement from baseline in ETDRS-DRSS. These findings demonstrate a comparable treatment effect and no significant difference between patients with and without DME.

Safety

The safety profile of Lucentis (ranibizumab injection) 0.3 mg was previously demonstrated in the original application, and subsequent supplements including S-106, approved February 6, 2015 for the treatment of diabetic retinopathy in patients with diabetic macular edema.

Deaths

**Table 7.3.1-1
 Deaths and Cause of Death Through 2 Years
 Safety-Evaluable Subjects**

Subject ID	Age / Sex	Study Day of Death	No. of RBZ injection prior to AE Onset	Baseline DME Status	SAE which Resulted in Death
One Study Eye - Ranibizumab					
(b) (6)	54/F	120	4	No	Congestive cardiac failure
(b) (6)	40/M	516	14	Yes	Chronic renal failure Left ventricular failure
(b) (6)	54/M	310	5	Yes	Cardiac failure Coronary artery disease Myelodysplastic syndrome
(b) (6)	66/M	610	14	No	Death, unknown cause
(b) (6)	44/M	373	8	No	Cardiac arrest Chronic kidney disease Hypoxic-ischemic encephalopathy
(b) (6)	53/F	491	6	Yes	History of angina Death, unknown cause
One Study Eye - PRP					
(b) (6)	43/M	538	5	Yes	Chronic renal failure, dialysis
(b) (6)	27/F	525	---	No	Complications of DM, gastroparesis
(b) (6)	74/F	167	1	Yes	Brain neoplasm
(b) (6)	54/M	126	---	No	Cardiac arrest

Subject ID	Age / Sex	Study Day of Death	No. of RBZ injection prior to AE Onset	Baseline DME Status	SAE which Resulted in Death
Two Study Eyes					
(b) (6)	62/M	514	15	Yes	Cerebrovascular accident
	53/M	120	5	No	Myocardial infarction
	58/M	469	11	No	Chronic renal failure, congestive heart failure
	48/F	408	11	No	Death, unknown cause

Fourteen deaths occurred during the 2-year conduct of Protocol S. The primary causes of death are not uncommon in the diabetic patient population.

Nonfatal Serious Adverse Events

Table 7.3.2 – 1
Ocular Serious Adverse Events in the Study Eye Through 2 Years
Safety Evaluable Eyes

MedDRA System Organ Class Preferred Term	Ranibizumab 0.5 mg			PRP		
	Overall N=191	Eyes with Baseline DME N=42	Eyes without Baseline DME N=149	Overall N=203	Eyes with Baseline DME N=46	Eyes without Baseline DME N=157
Total number of eyes with at least one adverse event	3 (1.6%)	1 (2.4%)	2 (1.3%)	2 (1.0%)	2 (4.3%)	0
Eye Disorders						
Vitreous hemorrhage	1 (0.5%)	1 (2.4%)	0	2 (1.0%)	2 (4.3%)	0
Sudden visual loss	1 (0.5%)	0	1 (0.7%)	0	0	0
Visual impairment	1 (0.5%)	0	1 (0.7%)	0	0	0
Vitreous floaters	1 (0.5%)	0	1 (0.7%)	0	0	0
Infections and infestations						
Endophthalmitis	1 (0.5%)	0	1 (0.7%)	0	0	0

Source: Module 2.7.3 CSR SCE, Table 9

Three subject eyes in the ranibizumab group experienced at least one ocular serious adverse event during the 2-year study period.

Table 7.3.2 – 2
Non-Ocular Serious Adverse Events Occurring in > 1 Subject in Any Treatment Group
Through 2 Years by Baseline DME Status Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye				Subjects with 2 Study Eyes	
	Ranibizumab		PRP		Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89		
Total number of subjects with at least 1 adverse event	13 (61.9%)	36 (44.4%)	9 (36.0%)	33 (37.1%)	10 (34.5%)	28 (46.7%)
Infections and infestations						
Pneumonia	1 (4.8%)	2 (2.5%)	0	2 (2.2%)	1 (3.4%)	3 (5.0%)
Localized infection	0	3 (3.7%)	0	1 (1.1%)	1 (3.4%)	1 (1.7%)
Sepsis	1 (4.8%)	1 (1.2%)	0	0	2 (6.9%)	1 (1.7%)
Cellulitis	0	2 (2.5%)	1 (4.0%)	1 (1.1%)	0	0
Osteomyelitis	0	2 (2.5%)	0	0	1 (3.4%)	1 (1.7%)
Urinary tract infection	0	1 (1.2%)	0	0	0	4 (6.7%)
General disorders and administration site conditions						
Chest pain	3 (14.3%)	5 (6.2%)	1 (4.0%)	2 (2.2%)	0	2 (3.3%)
Death	2 (9.5%)	1 (1.2%)	0	2 (2.2%)	0	2 (3.3%)
Asthenia	2 (9.5%)	2 (2.5%)	0	1 (1.1%)	0	0
Impaired healing	0	1 (1.2%)	0	2 (2.2%)	0	1 (1.7%)
Peripheral edema/swelling	0	3 (3.7%)	1 (4.0%)	0	0	1 (1.7%)
Surgical and medical procedures						
Stent placement	0	0	0	2 (2.2%)	0	2 (3.3%)
Toe amputation	1 (4.8%)	1 (1.2%)	0	0	1 (3.4%)	0
Coronary arterial stent insertion	0	0	0	0	0	2 (3.3%)
Surgery	0	0	0	0	1 (3.4%)	1 (1.7%)
Metabolism and nutrition disorders						
Dehydration	0	1 (1.2%)	1 (4.0%)	0	1 (3.4%)	1 (1.7%)
Diabetic ketoacidosis	0	3 (3.7%)	1 (4.0%)	0	0	0
Fluid overload	2 (9.5%)	1 (1.2%)	0	0	0	0
Hyperglycemia	0	0	0	0	0	3 (5.0%)
Ketoacidosis	0	1 (1.2%)	0	0	1 (3.4%)	0
Cardiac disorders						
Cardiac failure congestive	2 (9.5%)	4 (4.9%)	1 (4.0%)	1 (1.1%)	0	2 (3.3%)
Myocardial infarction ^a	1 (4.8%)	1 (1.2%)	0	3 (3.4%)	0	3 (5.0%)
Coronary artery disease	1 (4.8%)	2 (2.5%)	0	0	0	0

Deputy Division Director Summary Review
 BLA 125156 Supplement 114, Lucentis (ranibizumab injection)

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye				Subjects with 2 Study Eyes	
	Ranibizumab		PRP		Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89		
Cardiac arrest	1 (4.8%)	1 (1.2%)	0	0	0	0
Coronary artery stenosis	1 (4.8%)	0	0	0	0	1 (1.7%)
Renal and urinary disorders						
Acute kidney injury	0	5 (6.2%)	1 (4.0%)	0	1 (3.4%)	2 (3.3%)
Renal failure	3 (14.3%)	2 (2.5%)	1 (4.0%)	1 (1.1%)	0	2 (3.3%)
Chronic kidney disease	1 (4.8%)	1 (1.2%)	1 (4.0%)	1 (1.1%)	0	0
Nephropathy	2 (9.5%)	0	0	0	0	1 (1.7%)
Renal impairment	0	2 (2.5%)	0	1 (1.1%)	0	0
Nephrolithiasis	0	0	0	0	0	2 (3.3%)
Nervous system disorders						
Cerebrovascular accident	0	3 (3.7%)	2 (8.0%)	2 (2.2%)	1 (3.4%)	0
Syncope	1 (4.8%)	2 (2.5%)	0	0	0	0
Hypoxic-ischemic encephalopathy	1 (4.8%)	1 (1.2%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	4 (19.0%)	1 (1.2%)	1 (4.0%)	4 (4.5%)	0	2 (3.3%)
Cough	1 (4.8%)	1 (1.2%)	0	3 (3.4%)	0	0
Oropharyngeal pain	0	1 (1.2%)	0	2 (2.2%)	0	0
Injury, poisoning and procedural complications						
Foot fracture	2 (9.5%)	1 (1.2%)	1 (4.0%)	0	0	0
Fall	0	0	1 (4.0%)	1 (1.1%)	1 (3.4%)	0
Vascular disorders						
Hypertension	2 (9.5%)	2 (2.5%)	0	1 (1.1%)	1 (3.4%)	2 (3.3%)
Arterial occlusive disease	0	0	0	0	0	2 (3.3%)
Hypotension	0	0	0	0	0	2 (3.3%)
Gastrointestinal disorders						
Vomiting	0	4 (4.9%)	2 (8.0%)	0	1 (3.4%)	1 (1.7%)
Nausea	0	4 (4.9%)	2 (8.0%)	0	0	0
Abdominal pain	0	4 (4.9%)	0	0	0	0
Impaired gastric emptying	0	0	2 (8.0%)	1 (1.1%)	0	0
Investigations						
Blood glucose increased	0	2 (2.5%)	0	0	1 (3.4%)	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	0	1 (1.2%)	0	3 (3.4%)	0	0

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye				Subjects with 2 Study Eyes	
	Ranibizumab		PRP		Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89		
Skin and subcutaneous tissue disorders						
Diabetic foot	0	2 (2.5%)	0	0	1 (3.4%)	0
Skin ulcer	0	0	0	0	2 (6.9%)	0
Ear and labyrinth disorders						
Vertigo	0	0	0	3 (3.4%)	0	0

Source: Module 2.7.3 SCS Table 6

a Includes adverse events: myocardial infarction and acute myocardial infarction **b** Included adverse event preferred terms of cerebrovascular accident and ischemic stroke.

Serious non-ocular adverse events occurred in 44% of subjects in the ranibizumab-1 study eye subgroup without baseline DME. The most common non-ocular serious adverse events were chest pain, acute kidney injury, congestive heart failure, and pneumonia.

Common Adverse Events – Ocular and Nonocular

Table 7.4.1-1
Ocular Adverse Events in the Study Eye Occurring in ≥ 10% of Eyes in Any Treatment Group Through 2 Years Safety Evaluable Eyes

MedDRA System Organ Class Preferred Term	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Total number of eyes with at least 1 adverse event	152 (79.6%)	36 (85.7%)	116 (77.9%)	164 (80.8%)	39 (84.4%)	125 (79.6%)
Vitreous floaters	54 (28.3%)	8 (19.0%)	46 (30.9%)	56 (27.6%)	13 (28.3%)	43 (27.4%)
Vitreous hemorrhage	39 (20.4%)	10 (23.8%)	29 (19.5%)	54 (26.6%)	10 (21.7%)	44 (28.0%)
Vision blurred	32 (16.8%)	9 (21.4%)	23 (15.4%)	54 (26.6%)	15 (32.6%)	39 (24.8%)
Visual acuity reduced	26 (13.6%)	8 (19.0%)	18 (12.1%)	38 (18.7%)	12 (26.1%)	26 (16.6%)
Eye pain	27 (14.1%)	7 (16.7%)	20 (13.4%)	30 (14.8%)	4 (8.7%)	26 (16.6%)
Dry eye	16 (8.4%)	4 (9.5%)	12 (8.1%)	15 (7.4%)	6 (13.0%)	9 (5.7%)
Visual impairment	14 (7.3%)	4 (9.5%)	10 (6.7%)	15 (7.4%)	2 (4.3%)	13 (8.3%)
Conjunctival hemorrhage	21 (11.0%)	5 (11.9%)	16 (10.7%)	7 (3.4%)	4 (8.7%)	3 (1.9%)
Cataract	10 (5.2%)	4 (9.5%)	6 (4.0%)	16 (7.9%)	4 (8.7%)	12 (7.6%)
Retinal detachment	9 (4.7%)	1 (2.4%)	8 (5.4%)	17 (8.4%)	4 (8.7%)	13 (8.3%)
Eye pruritus	12 (6.3%)	3 (7.1%)	9 (6.0%)	12 (5.9%)	3 (6.5%)	9 (5.7%)
Lacrimation increased	11 (5.8%)	4 (9.5%)	7 (4.7%)	12 (5.9%)	3 (6.5%)	9 (5.7%)

MedDRA System Organ Class Preferred Term	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Retinal hemorrhage	13 (6.8%)	3 (7.1%)	10 (6.7%)	10 (4.9%)	2 (4.3%)	8 (5.1%)
Photopsia	8 (4.2%)	0	8 (5.4%)	13 (6.4%)	5 (10.9%)	8 (5.1%)
Eye irritation	13 (6.8%)	2 (4.8%)	11 (7.4%)	7 (3.4%)	3 (6.5%)	4 (2.5%)
Eye disorder	7 (3.7%)	1 (2.4%)	6 (4.0%)	10 (4.9%)	3 (6.5%)	7 (4.5%)
Macular fibrosis	6 (3.1%)	2 (4.8%)	4 (2.7%)	11 (5.4%)	6 (13.0%)	5 (3.2%)
Unevaluable event	21 (11.0%)	6 (14.3%)	15 (10.1%)	24 (11.8%)	9 (19.6%)	15 (9.6%)

Source: Module 2.7.3 SCS Table 6

The frequency of ocular adverse events was similar between the ranibizumab with and without baseline DME treatment groups, and between ranibizumab and PRP treatment groups.

The most common ocular adverse events in the ranibizumab without baseline DME treatment group were vitreous floaters, vitreous hemorrhage, blurred vision, eye pain, visual acuity reduced and conjunctival hemorrhage. All of these adverse events except vitreous hemorrhage are included in the Lucentis package insert.

**Table 7.4.1-2
 Non-Ocular Adverse Events Occurring in ≥ 10% of Eyes in Any Treatment Group Through 2 Years by Baseline DME Safety Evaluable Subjects**

MedDRA System Organ Class Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Total number of subjects with at least 1 adverse event	45 (90.0%)	128 (90.8%)	20 (80.0%)	71 (79.8%)
Infections and infestations				
Nasopharyngitis	10 (20.0%)	18 (12.8%)	3 (12.0%)	7 (7.9%)
Influenza	7 (14.0%)	13 (9.2%)	2 (8.0%)	6 (6.7%)
General disorders and administration site conditions				
Unevaluable event	3 (6.0%)	5 (3.5%)	3 (12.0%)	1 (1.1%)
Nervous system disorders				
Headache	6 (12.0%)	20 (14.2%)	3 (12.0%)	11 (12.4%)
Respiratory, thoracic and mediastinal disorders				
Cough	5 (10.0%)	19 (13.5%)	1 (4.0%)	6 (6.7%)
Dyspnea	5 (10.0%)	10 (7.1%)	1 (4.0%)	6 (6.7%)

MedDRA System Organ Class Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Gastrointestinal disorders				
Nausea	5 (10.0%)	15 (10.6%)	4 (16.0%)	6 (6.7%)
Vomiting	3 (6.0%)	14 (9.9%)	3 (12.0%)	3 (3.4%)
Injury, poisoning and procedural complications				
Fall	7 (14.0%)	8 (5.7%)	3 (12.0%)	4 (4.5%)
Vascular disorders				
Hypertension	12 (24.0%)	25 (17.7%)	6 (24.0%)	14 (15.7%)
Metabolism and nutrition disorders				
Diabetes mellitus inadequate control	2 (9.5%)	10 (12.3%)	4 (16.0%)	6 (6.7%)
Renal and urinary disorders				
Nephropathy	7 (14.0%)	11 (7.8%)	2 (8.0%)	7 (7.9%)
Renal disorder	2 (4.0%)	6 (4.3%)	3 (12.0%)	2 (2.2%)
Chronic kidney disease	1 (2.0%)	4 (2.8%)	3 (12.0%)	1 (1.1%)
Cardiac disorders				
Coronary artery disease	6 (12.0%)	6 (4.3%)	0	2 (2.2%)
Psychiatric disorders				
Depression	0	2 (1.4%)	3 (12.0%)	4 (4.5%)

Source: Module 2.7.3 SCS Table 7; March 24, 2017 submission in response to Information Request #4

Ninety percent of ranibizumab subjects and eighty percent of PRP subjects experienced at least one adverse event. The rates of non-ocular adverse events were similar in ranibizumab and PRP subjects.

The most common non-ocular adverse events in ranibizumab subjects which occurred more frequently in the ranibizumab group were hypertension, nasopharyngitis, headache, influenza, nephropathy, nausea, and fall.

Antiplatelet Trialists' Collaboration Events

Antiplatelet Trialists' Collaboration events (vascular deaths, unknown cause deaths, non-fatal myocardial infarctions, non-fatal cerebrovascular accidents) were reported in 4 (19.0%) subjects in the ranibizumab- study eye subgroup with baseline DME and 6 (7.4%) subjects without baseline DME. In the 2 study eyes group, APTC events were reported in 1 (3.4%) subject with baseline DME and 5 (8.3%) subjects without baseline DME. In the PRP-1 study eye group, APTC events were reported in 2 (8.0%) subjects with baseline DME and 7 (7.9%) subjects without baseline DME.

**Table 7.3.4-1 Deaths, Myocardial Infarctions, and Cerebrovascular Accidents
 Through 2 Years by Baseline DME Status
 Safety Evaluable Subjects**

Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Any Event	6 (12.0%)	13 (9.2%)	4 (16.0%)	8 (9.0%)
Deaths				
Overall	4 (8.0%)	6 (4.3%)	2 (8.0%)	2 (2.2%)
Vascular	1 (2.0%)	2 (1.4%)	0	1 (1.1%)
Non-vascular	1 (2.0%)	2 (1.4%)	2 (8.0%)	1 (1.1%)
Unknown cause	2 (4.0%)	2 (1.4%)	0	0
MI or CVA				
Overall	3 (6.0%)	8 (5.7%)	2 (8.0%)	6 (6.7%)
MI				
Overall	2 (4.0%)	4 (2.8%)	0	4 (4.5%)
Fatal	0	1 (0.7%)	0	0
Non-fatal	2 (4.0%)	3 (2.1%)	0	4 (4.5%)
CVA				
Overall	1 (2.0%)	4 (2.8%)	2 (8.0%)	2 (2.2%)
Fatal	1 (2.0%)	0	0	0
Non-fatal	0	4 (2.8%)	2 (8.0%)	2 (2.2%)
APTC events (vascular deaths, unknown cause deaths, non-fatal MIs, non-fatal CVAs)	5 (10.0%)	11 (7.8%)	2 (8.0%)	7 (7.9%)

Note: Subjects with 2 study eyes enrolled are included in the Ranibizumab group. Subjects with 2 study eyes enrolled are considered to have baseline DME if at least 1 study eye has baseline DME.

The proportion of patients who experienced APTC events was the same for the ranibizumab (8%) and PRP (8%) treatment groups.

Safety Update

Genentech reviewed the safety data of subjects without baseline diabetic macular edema (DME) in the ranibizumab arm in the ongoing Protocol S study with a data cut off of December 6, 2016. The types of ocular and non-ocular adverse events observed were consistent with the safety profile observed for this subgroup at the primary endpoint at 2 years and the well-established safety profile of Lucentis. No additional safety information for Lucentis in patients with diabetic retinopathy (DR) without DME has become available from other clinical studies.

Safety Summary

The Clinical Study Report submitted within this Supplemental BLA 125156 for Study Protocol S (Protocol ML27976) in association with the safety data which supported the previously submitted indications supports the safety of ranibizumab 0.5 mg injection in the treatment of patients with diabetic retinopathy.

The most common ocular adverse events in the ranibizumab without baseline DME treatment group were vitreous floaters, vitreous hemorrhage, blurred vision, eye pain, visual acuity reduced and conjunctival hemorrhage. All of these adverse events except vitreous hemorrhage are included in the Lucentis package insert.

The most common non-ocular adverse events in ranibizumab subjects which occurred more frequently in the ranibizumab group were hypertension, nasopharyngitis, headache, influenza, nephropathy, nausea, and fall.

7. Advisory Committee Meeting

There were no issues raised in this supplement that were thought to benefit from an Advisory Committee Meeting discussion.

8. Pediatrics

The applicant requested and received a waiver of the pediatric study requirements for the original Biologics License Application. The FDA agreed to Genentech's request for a Pediatric Waiver (PeRC meeting held 2/8/2017). The waiver was requested because the disease under study (diabetic retinopathy) very rarely occurs in the pediatric age group.

9. Other Relevant Regulatory Issues

DSI

A routine Division of Scientific Investigations (DSI) audit was requested. Protocol ML27976 was conducted at 57 clinical sites in the U.S. Planned enrollment was a minimum of 380 eyes with 394 eyes actually randomized to study. Dr. Browning's site was selected for inspection because of its enrollment of a relatively large numbers of subjects.

The primary efficacy endpoint was the change in visual acuity from baseline to 2 years. This data was contained in Listing H and was confirmed for every study subject. OCT values were determined by the site and entered into the eCRFs. The OCT report was then sent to the reading center which determined its own value. Diabetic retinopathy (DR) scores were assigned by the reading center.

The data listings provided by the applicant were reportedly those values determined by the reading center. These values were not reported back to the study site. According to the study site, a review committee monitored differences in values assigned by the study site and the reading center.

Unusual differences would be investigated and additional training would be provided to the sites and/or reading center as needed. For this study, the differences in values between those determined by the study site and the reading center were not considered unusual.

A Form FDA 483 was not issued at the conclusion of the inspection. Notwithstanding the discrepant OCT results, the results of the clinical investigator inspection indicate that Dr. Browning's study conduct appears to have been adequate, and the data otherwise generated by this site appear acceptable in support of the respective indication.

As described in the Clinical Team Leader's review, the applicant provided detailed responses on 3/15/2017 (SDN-901) to the Agency's information request regarding the discrepancies in OCT values. The detailed process by which central readings were handled for Protocol S was provided; the applicant's description is satisfactory. The OCT value recorded on the CRF was used for immediate DME treatment decisions and was not updated to reflect the JCHR or the Duke Reading Center OCT values. The applicant's explanation for the OCT discrepancies is acceptable.

FINANCIAL DISCLOSURE

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

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review for S-114 on 3/6/2017. Their comments regarding the package insert are addressed in the final labeling. The proposed container label, carton labeling, and Prescribing Information (PI) were found acceptable from a medication error perspective.

DDMAC

The Office of Prescription Drug Promotion (OPDP) finalized a review on 3/20/17. Their comments are addressed in the final labeling.

ADL

The Associate Director for Labeling finalized a review dated 4/11/2017. The ADL suggested removing the subheadings in Section 1 and converting the list of indications to a bulleted list. This suggestion was not incorporated since it is inconsistent with the approved labeling for products with multiple indications.

10. Labeling

The review team is in agreement with the revised proposed labeling submitted April 11, 2017 and included below.

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

11. Conclusions/Action

BLA 125156 for Lucentis (ranibizumab injection), Supplement 114, will be approved for the treatment of patients with diabetic retinopathy (DR) with the package insert labeling submitted by Genentech, Inc., on 4/11/2017.

RISK BENEFIT ASSESSMENT:

The benefits of Lucentis (ranibizumab injection) for the recommended indication outweigh the associated risks described below.

Based on the agreed upon efficacy measure (i.e., the proportion of eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 2 years) Eyes in the ranibizumab group experienced clinically meaningful and consistent improvements of ≥ 3 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

The most common ocular adverse events in the ranibizumab without baseline DME treatment group were vitreous floaters, vitreous hemorrhage, blurred vision, eye pain, visual acuity reduced and conjunctival hemorrhage. All of these adverse events except vitreous hemorrhage are included in the Lucentis package insert. Vitreous hemorrhages are likely to be a consequence of diabetic retinopathy. The most common non-ocular adverse events in ranibizumab subjects which occurred more frequently in the ranibizumab group were hypertension, nasopharyngitis, headache, influenza, nephropathy, nausea, and falls.

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

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/s/

WILEY A CHAMBERS
04/15/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: sBLA 125156/s-114

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

Solomon Chefo
Sarah Kennett
Wiley Chambers
Rhea Lloyd
William Boyd
Yan Wang

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 12, 2017
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	125156
Applicant	Genentech, Inc.
Date of Submission	October 18, 2016
PDUFA Goal Date	April 18, 2017
Type of Application	Supplement 114
Name	Lucentis (ranibizumab injection)
Dosage forms / Strength	solution for intravitreal injection
Proposed New Indication(s)	For the treatment of patients with diabetic retinopathy
Recommended:	Recommended for Approval

1. Introduction

In this supplemental BLA, Genentech seeks to update the Lucentis labeling with a new indication, the treatment of patients with diabetic retinopathy.

Lucentis (ranibizumab injection) is currently approved for the treatment of diabetic retinopathy in patients with diabetic macular edema. The purpose of this efficacy supplement is to demonstrate safety and efficacy in patients with diabetic retinopathy without diabetic macular edema.

Diabetic retinopathy (DR) may occur at any time during the disease course as a complication of both Type 1 and Type 2 diabetes mellitus, although significant retinopathy rarely occurs within the first ten years following the diagnosis of diabetes. 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.

Progression of DR can be measured in discrete steps as described by the ETDRS DR Severity Scale¹. This scale is well established for objective quantification of retinopathy severity and a

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

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

Protocol S was designed to determine the relative efficacy of ranibizumab 0.5 mg injection vs. panretinal photocoagulation (PRP) for the treatment of diabetic retinopathy which was the previous standard of care treatment. Because DME is a manifestation of DR, many enrolled subjects also had DME. Randomized subjects were stratified based on DME status at baseline.

Thus, data from Protocol S was proposed to address whether ranibizumab intravitreal injections would be effective in patients with DR without DME. Demonstration of efficacy in this patient population, together with the previous studies might support broadening the indication to all patients with diabetic retinopathy.

2. Background

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.

Reference is also made to the following Supplemental BLAs for Lucentis (ranibizumab injection):

- S-053, for Lucentis (ranibizumab injection), 0.5 mg approved on June 22, 2010, for the treatment of patients with macular edema following retinal vein occlusion.
- S-076, for Lucentis (ranibizumab injection), 0.3 mg approved on August 10, 2012, for the treatment of patients with diabetic macular edema.
- S-106, for Lucentis (ranibizumab injection), 0.3 mg approved on February 6, 2015, for the treatment of diabetic retinopathy in patients with diabetic macular edema.
- S-111, for Lucentis (ranibizumab injection), 0.5 mg approved on January 5, 2017, for the treatment of myopic choroidal neovascularization.

In this supplemental BLA, Genentech seeks to update the Lucentis labeling with a new indication, the treatment of patients with diabetic retinopathy (DR).

The Jaeb Center for Health Research (JCHR) was the sponsor of Protocol S and the coordinating center for the Diabetic Research Clinical Research Network (DRCR.net). The JCHR conducted the study, and the DRCR.net supported the identification, design, and implementation of the Protocol S study. This collaboration is referred to as JCHR (DRCR.net).

Genentech did have an opportunity to review JCHR (DRCR.net)'s protocol and provide comments. However, JCHR (DRCR.net) was under no obligation to incorporate those

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.

suggestions. Genentech was not involved in the conduct of the study but did provide ranibizumab and funds to the JCHR to defray the study's costs.

September 1, 2015 – A Type B, teleconference meeting was held with Genentech to discuss a proposal to expand the diabetic retinopathy (DR) in patients with diabetic macular edema (DME) indication to include all patients with diabetic retinopathy regardless of DME status. The basis for this supplement submission was to be an analysis of retinopathy outcomes data from the Diabetic Retinopathy Clinical Research Network (DRCR.net)-sponsored study, Protocol S, which studied the treatment of DR regardless of the presence of DME using ranibizumab and panretinal photocoagulation (PRP).

At that time, the Division expressed concerns about using the data from Protocol S to support a supplemental BLA submission and suggested that the following concerns should be addressed:

- Protocol S was not designed to assess the DR endpoints as a primary endpoint or in a manner which controlled potential Type I error. An attempt to control multiplicity for endpoints used to support your submission will be post-hoc since the analyses are completed. However, an explanation should be provided regarding why the observed treatment effect for the endpoints included in your submission is not likely due to chance alone.
- In Protocol S, the comparator arm, panretinal photocoagulation, could introduce potential bias due to the inability to adequately mask the treatment groups. The impact of this potential bias on the data should be addressed.
- Ranibizumab 0.3 mg monthly is the approved dose and dosing regimen for the diabetic retinopathy with diabetic macular edema indication. Protocol S included only ranibizumab 0.5 mg dosed on a PRN dosing schedule. It is not clear how a bridge can be established from the ranibizumab 0.5 mg PRN dosing regimen to ranibizumab 0.3 mg monthly dosing regimen.
- The use of Protocol S to compare patients with diabetic retinopathy and macular edema to patients with diabetic retinopathy without macular edema has a number of limitations (e.g., post-hoc analysis, assumes treatment effect of an unapproved regimen), and has not been demonstrated in other studies. These limitations should be addressed.

3. CMC

From the Office of Biotechnology, Division of Monoclonal Antibodies, Memorandum of Review finalized 3/19/2017:

Commercial Lucentis was used in the Protocol S study, and the claim of categorical exemption from the environmental assessment is acceptable.

There are no CMC-related approvability issues.

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review finalized 12/27/2016:

The intended dose for Lucentis in the treatment of diabetic retinopathy is 0.3 mg (0.05 mL) administered by intravitreal injection once a month. This dosing regimen is the same previously approved by the FDA for diabetic retinopathy in patients with diabetic macular edema. No new nonclinical studies were submitted with this supplemental BLA. As such, there are no new concerns from the nonclinical perspective.[Note: Previous studies supported the approval of the 0.3 dose for the treatment of diabetic retinopathy in patients with diabetic macular edema, but the applicant never requested the indication for this dose.]

5. Clinical Pharmacology/Biopharmaceutics

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

6. Sterility Assurance

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

7. Clinical/Statistical - Efficacy

From the Medical Officer Review finalized 3/29/2017:

Table of Studies/Clinical Trials

Study	Phase	Design (Sites)	Population	No. of Subjects Enrolled	Treatment Frequency and Duration
Protocol S (Protocol ML27976)	3	Multicenter, randomized, single-masked, active treatment-controlled USA	Adult patients with proliferative diabetic retinopathy	305 subjects (394 eyes) RBZ group (n=191 eyes) PRP group (n=203 eyes)	RBZ group: 0.5 mg IVT injection at randomization/baseline, 4-, 8-, and 12-week follow-up visits. Beginning at 16-week visit, eyes were evaluated for retreatment based on appearance of neovascularization. PRP group: A full session of 1200-1600 burns using 500 micron burns on the retina or the equivalent area treated when using indirect laser delivery systems was completed within 56 days of randomization. Study eyes in the PRP group could receive supplemental PRP if neovascularization worsened during the study following completion of the initial PRP session. Eyes in both groups could receive ranibizumab as needed for DME, at baseline or if DME developed during the course of the study.

I. Analysis of Main Efficacy Measure

In the original statistical analysis, the primary efficacy variable was the mean change in visual acuity at 2 years from baseline. That data is presented in a subsequent section, **III. Additional Efficacy Issues/Analyses**

For this supplemental BLA submission for the treatment of diabetic retinopathy independent of baseline DME studies, the redefined main efficacy measure is: the proportion of eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 2 years.

Table 6.1.4-1

Proportion of Eyes with ≥ 3 -Step Improvement from Baseline in Ranibizumab Group in ETDRS-DRSS by Baseline DME Status (Eyes with a Valid ETDRS-DRSS at Baseline)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
AT 1 YEAR		
LOCF		
N	41	148
n (%)	13 (31.7%)	41 (27.7%)
95% CI for percentage	(17.5%, 46.0%)	(20.5%, 34.9%)
Difference in percentages		4.0%
95% CI for difference		(-12.0%, 20.0%)
Observed		
N	33	122
n (%)	13 (39.4%)	41 (33.6%)
95% CI for percentage	(22.7%, 56.1%)	(25.2%, 42.0%)
Difference in percentages		5.8%
95% CI for difference		(-12.9%, 24.4%)
Multiple Imputation		
N	41	148
n (%)	16 (40.6%)	54 (36.8%)
95% CI for percentage	(23.8%, 57.4%)	(28.4%, 45.1%)
Difference in percentages		3.9%
95% CI for difference		(-15.3%, 23.0%)
AT 2 YEARS		
LOCF		
N	41	148
n (%)	13 (31.7%)	42 (28.4%)
95% CI for percentage	(17.5%, 46.0%)	(21.1%, 35.6%)
Difference in percentages		3.3%
95% CI for difference		(-12.7%, 19.3%)
Observed		
N	27	116
n (%)	10 (37.0%)	38 (32.8%)
95% CI for percentage	(18.8%, 55.3%)	(24.2%, 41.3%)
Difference in percentages		4.3%
95% CI for difference		(-15.8%, 24.4%)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
Multiple Imputation		
N	41	148
n (%)	16 (40.2%)	51 (35.1%)
95% CI for percentage	(22.9%, 57.6%)	(26.9%, 43.4%)
Difference in percentages		5.1%
95% CI for difference		(-13.8%, 24.0%)

Source: Module 2.7.3 SCE Table 9 and 10; Response to IR #4 dated March 24, 2017.

Note: ICs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputation, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 3 -step improvement.

Eyes in the ranibizumab group experienced clinically meaningful and consistent improvements of ≥ 3 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

In the ranibizumab treatment group at the 2 year time point, the proportion of eyes with baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 32% - 40%; while the proportion of eyes without baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 28% - 35%.

Sensitivity Analysis

**Table 6.1.4-2
 Proportion of Eyes with \geq 2-Step and \geq 3-Step Improvement from Baseline in ETRDS-DRSS:
 Ranibizumab Groups with versus without DME at Baseline in Phase 3 Studies**

	\geq 2-Step Improvement			\geq 3-Step Improvement		
	0.5 mg RBZ PRN No DME % (n/N) 95% CI	DME % (n/N) 95% CI	Difference (95% CI)	0.5 mg RBZ PRN No DME % (n/N) 95% CI	DME % (n/N) 95% CI	Difference (95% CI)
Week 104	37.8 (56/148) (30.0, 45.7)	58.5 (24/41) (43.5, 73.6)	20.7 (3.7, 37.7)	28.4 (42/148) (21.1, 35.6)	31.7 (13/41) (17.5, 46.0)	3.3 (-12.7, 19.3)
Study FVF4168g – RIDE^{b, c}	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)
Month 24	4.0 (5/124) (0.6, 7.5)	36.1 (43/119) (27.5, 44.8)	32.0 (22.8, 41.2)	2.4 (3/124) (0.0, 5.1)	17.6 (21/119) (10.8, 24.5)	15.0 (7.8, 22.2)
Study FVF4170g – RISE^{b, c}	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)
Month 24	7.0 (8/115) (2.3, 11.6)	35.7 (41/115) (26.9, 44.4)	28.3 (18.9, 37.7)	0 (0/0) (0.0, 0.0)	11.3 (13/115) (5.5, 17.1)	11.7 (5.9, 17.4)

a S-114, Response to IR #4 dated March 24, 2017. CIs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputation, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for \geq 3-step improvement. LOCF

b Source: S-106 Module 5.3.5.3 ISE Tables 12 and 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 (\leq 55, $>$ 55 letters), baseline HbA1c (\leq 8%, $>$ 8%), and prior therapy for DME in the study eye (yes, no). 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.

At 2 years, the treatment group difference of 0.5 mg ranibizumab monthly compared to sham treatment was 28 – 32% in the RIDE study for the proportion of patients who experienced a ≥ 2 -step improvement from baseline in ETDRS-DRSS and 12 - 15% in the RISE study for the proportion of patients who experienced a ≥ 3 -step improvement from baseline in ETDRS-DRSS.

The lower bound of the confidence intervals of the differences in RIDE and RISE studies for the proportion of patients who experienced a ≥ 2 -step improvement from baseline in ETDRS-DRSS were 19 – 23%. The lower bound of the confidence intervals of the differences in RIDE and RISE studies for the proportion of patients who experienced a ≥ 3 -step improvement from baseline in ETDRS-DRSS were 6 – 8%.

At 2 years in Protocol S, the 0.5 mg ranibizumab PRN treatment group differences for patients without DME compared to those with DME was 21% for the proportion of patients who experienced a ≥ 2 -step improvement from baseline in ETDRS-DRSS and 3% in the for the proportion of patients who experienced a ≥ 3 -step improvement from baseline in ETDRS-DRSS. These findings demonstrate a comparable treatment effect and no significant difference between patients with and without DME.

II. New Supportive Endpoint Analyses

Table 6.1.5-1
Proportion of Eyes with ≥ 2 -Step Improvement from Baseline in Ranibizumab Group in ETDRS-DRSS by Baseline DME Status
(Eyes with a Valid ETDRS-DRSS at Baseline)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
AT 1 YEAR		
LOCF		
N	41	148
n (%)	20 (48.8%)	59 (39.9%)
95% CI for percentage	(33.5%, 64.1%)	(32.0%, 47.8%)
Difference in percentages		8.9%
95% CI for difference		(-8.3%, 26.1%)
Observed		
N	33	122
n (%)	20 (60.6%)	59 (48.4%)
95% CI for percentage	(43.9%, 77.3%)	(39.5%, 57.2%)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
Difference in percentages		12.2%
95% CI for difference		(-6.6%, 31.1%)
Multiple Imputation		
N	41	148
n (%)	25 (61.1%)	76 (51.7%)
95% CI for percentage	(44.7%, 77.5%)	(43.2%, 60.2%)
Difference in percentages		9.4%
95% CI for difference		(-9.0%, 27.8%)
AT 2 YEARS		
LOCF		
N	41	148
n (%)	24 (58.5%)	56 (37.8%)
95% CI for percentage	(43.4%, 73.6%)	(30.0%, 45.7%)
Difference in percentages		20.7%
95% CI for difference		(3.7%, 37.7%)
Observed		
N	27	116
n (%)	18 (66.7%)	49 (42.2%)
95% CI for percentage	(48.9%, 84.4%)	(33.3%, 51.2%)
Difference in percentages		24.4%
95% CI for difference		(4.5%, 44.3%)
Multiple Imputation		
N	41	148
n (%)	27 (66.3%)	68 (46.2%)
95% CI for percentage	(49.4%, 83.3%)	(37.5%, 54.9%)
Difference in percentages		20.1%
95% CI for difference		(0.6%, 39.6%)

Source: Module 2.7.3 SCE Table 9 and 10; Response to IR #4 dated March 24, 2017.

Note: ICs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputations, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 3 -step improvement.

Eyes in the ranibizumab group experienced clinically meaningful and consistent improvements of ≥ 2 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

In the ranibizumab treatment group at the 2 year time point, the proportion of eyes with baseline DME that experienced a ≥ 2 -step improvement from baseline in the ETDRS-DRSS ranged from 59% - 67%; while the proportion of eyes without baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 38% - 46%.

Sensitivity Analysis

Table 6.1.5-2
Proportion of Eyes with Improvement of ≥ 2 -Step in ETDRS-DRSS
from PDR at Baseline to NPDR at 1 Year and 2 Years by Baseline DME Status
(Eyes with PDR and a Valid ETDRS-DRSS at Baseline; LOCF)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
1 Year (Week 52)		
N	38	132
n (%)	10 (26.3%)	38 (28.8%)
95% CI for percentage ^a	(12.3%, 40.3%)	(21.1%, 36.5%)
Difference in percentages		-2.5%
95% CI for difference ^a		(-18.5%, 13.5%)
2 Years (Week 104)		
N	38	132
n (%)	9 (23.7%)	37 (28.0%)
95% CI for percentage ^a	(10.2%, 37.2%)	(20.4%, 35.7%)
Difference in percentages		-4.3%
95% CI for difference ^a		(-19.9%, 11.2%)

Source: S-114, Response to IR #4 dated March 24, 2017.

PDR is defined as an ETDRS-DRSS score ≥ 60 ; NPDR is defined as an ETDRS-DRSS score < 60 .

^a CIs for percentages and differences in percentages are based on normal approximation for binomial proportions.

There was no significant difference in the proportion of eyes with ≥ 2 -step improvement in ETDRS-DRSS from PDR at Baseline to NPDR at 1 Year and 2 Years by baseline DME status.

A similar proportion of patients in the ranibizumab treated group with and without DME experienced and improvement of in ETDRS-DRSS from PDR at baseline to NPDR.

III. Additional Efficacy Issues/Analyses

In the original statistical analysis, the primary efficacy variable was the mean change in best corrected visual acuity from baseline in the Study Eye at 2 years.

Primary Efficacy Results – Original Statistical Analysis Plan

Table 6.1.10-1
Mean Change in Best Corrected Visual Acuity (ETDRS letters) from Baseline
in the Study Eye at 2 Years (LOCF) Randomized Eyes

	Ranibizumab 0.5 mg N=191	PRP Total N=203
Baseline		
n	191	203
Mean (SD)	75.0 (12.8)	75.2 (12.5)
Median	77.0	78.0
Min – Max	0.0- 12.0	-4.0 – 7.0
Week 104 (2 Years)		
n	191	203
Mean (SD)	2.7 (17.8)	-0.7 (15.5)
Median (SE)	5.0 (1.3)	1.0 (1.1)
95% CI for mean	(0.2, 5.2)	(-2.8, 1.5)
Difference in means		3.4
95% CI for difference		(0.1, 6.6)
Test for Treatment Difference		
Student t-test (unstratified)		0.0460
ANOVA t-test (stratified)		0.0382

Source: Module 5.3.5.1 CSR ML27976 Section 5.2.1 Table 16
 Stratification variables in stratified analyses: baseline DME status and number of eyes enrolled. All CIs are 2-sided. CIs for means and differences in means are based on Student t-distribution (Unstratified). Estimates and CIs for LS means and differences in LS means are from the ANOVA model (stratified).

The study met the primary efficacy endpoint as pre-specified in the original statistical analysis plan. The mean change in visual acuity from baseline in the study eye at 2 years was statistically significant in favor of the ranibizumab treatment group when compared to PRP treatment group.

Efficacy Summary Statement

For the redefined main efficacy measure (i.e., the proportion of eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 2 years):

Eyes in the ranibizumab group experienced clinically meaningful and consistent improvements of ≥ 3 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

In the ranibizumab treatment group at the 2 year time point, the proportion of eyes with baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 32% - 40%; while the proportion of eyes without baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 28% - 35%.

For the primary efficacy variable specified in the original statistical analysis (i.e., the mean change in best corrected visual acuity from baseline in the Study Eye at 2 years):

The mean change in visual acuity from baseline in the study eye at 2 years was statistically significant in favor of the ranibizumab treatment group when compared to PRP treatment group.

8. Safety

From the Medical Officer Review finalized 3/29/2017:

This review of safety describes the safety profile of Lucentis (ranibizumab injection) 0.5 mg for the treatment of patients with diabetic retinopathy independent of the presence of diabetic macular edema (DME). Data from the Phase 3, prospective, multicenter, randomized clinical trial Protocol S are included in this section.

The safety summary focuses on the ranibizumab without DME subgroup. There were approximately three times as many subjects without DME as with DME at baseline, therefore, direct group comparisons are problematic. Also, 54% of subjects in the PRP treatment groups received ranibizumab injections during the study thus confounding treatment group comparisons.

The safety profile of Lucentis (ranibizumab injection) 0.3 mg for the treatment of diabetic retinopathy in patients with diabetic macular edema was previously demonstrated in S-106, approved February 6, 2015.

Deaths

Table 7.3.1-1
Deaths and Cause of Death Through 2 Years
Safety-Evaluable Subjects

Subject ID	Age / Sex	Study Day of Death	No. of RBZ injection prior to AE Onset	Baseline DME Status	SAE which Resulted in Death
One Study Eye - Ranibizumab					
(b) (6)	54/F	120	4	No	Congestive cardiac failure
(b) (6)	40/M	516	14	Yes	Chronic renal failure Left ventricular failure
(b) (6)	54/M	310	5	Yes	Cardiac failure Coronary artery disease Myelodysplastic syndrome
(b) (6)	66/M	610	14	No	Death, unknown cause
(b) (6)	44/M	373	8	No	Cardiac arrest Chronic kidney disease Hypoxic-ischemic encephalopathy
(b) (6)	53/F	491	6	Yes	History of angina Death, unknown cause
One Study Eye - PRP					
(b) (6)	43/M	538	5	Yes	Chronic renal failure, dialysis
(b) (6)	27/F	525	---	No	Complications of DM, gastroparesis
(b) (6)	74/F	167	1	Yes	Brain neoplasm
(b) (6)	54/M	126	---	No	Cardiac arrest
Two Study Eyes					
(b) (6)	62/M	514	15	Yes	Cerebrovascular accident
(b) (6)	53/M	120	5	No	Myocardial infarction
(b) (6)	58/M	469	11	No	Chronic renal failure, congestive heart failure
(b) (6)	48/F	408	11	No	Death, unknown cause

Fourteen deaths occurred during the 2-year conduct of Protocol S. The primary causes of death are not uncommon in the diabetic patient population.

Nonfatal Serious Adverse Events

**Table 7.3.2 – 1
 Ocular Serious Adverse Events in the Study Eye Through 2 Years
 Safety Evaluable Eyes**

MedDRA System Organ Class Preferred Term	Ranibizumab 0.5 mg			PRP		
	Overall N=191	Eyes with Baseline DME N=42	Eyes without Baseline DME N=149	Overall N=203	Eyes with Baseline DME N=46	Eyes without Baseline DME N=157
Total number of eyes with at least one adverse event	3 (1.6%)	1 (2.4%)	2 (1.3%)	2 (1.0%)	2 (4.3%)	0
Eye Disorders						
Vitreous hemorrhage	1 (0.5%)	1 (2.4%)	0	2 (1.0%)	2 (4.3%)	0
Sudden visual loss	1 (0.5%)	0	1 (0.7%)	0	0	0
Visual impairment	1 (0.5%)	0	1 (0.7%)	0	0	0
Vitreous floaters	1 (0.5%)	0	1 (0.7%)	0	0	0
Infections and infestations						
Endophthalmitis	1 (0.5%)	0	1 (0.7%)	0	0	0

Source: Module 2.7.3 CSR SCE, Table 9

Three subject eyes in the ranibizumab group experienced at least one ocular serious adverse event during the 2-year study period.

Table 7.3.2 – 2
Non-Ocular Serious Adverse Events Occurring in > 1 Subject in Any Treatment Group
Through 2 Years by Baseline DME Status
Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye				Subjects with 2 Study Eyes	
	Ranibizumab		PRP		Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89		
Total number of subjects with at least 1 adverse event	13 (61.9%)	36 (44.4%)	9 (36.0%)	33 (37.1%)	10 (34.5%)	28 (46.7%)
Infections and infestations						
Pneumonia	1 (4.8%)	2 (2.5%)	0	2 (2.2%)	1 (3.4%)	3 (5.0%)
Localized infection	0	3 (3.7%)	0	1 (1.1%)	1 (3.4%)	1 (1.7%)
Sepsis	1 (4.8%)	1 (1.2%)	0	0	2 (6.9%)	1 (1.7%)
Cellulitis	0	2 (2.5%)	1 (4.0%)	1 (1.1%)	0	0
Osteomyelitis	0	2 (2.5%)	0	0	1 (3.4%)	1 (1.7%)
Urinary tract infection	0	1 (1.2%)	0	0	0	4 (6.7%)
General disorders and administration site conditions						
Chest pain	3 (14.3%)	5 (6.2%)	1 (4.0%)	2 (2.2%)	0	2 (3.3%)
Death	2 (9.5%)	1 (1.2%)	0	2 (2.2%)	0	2 (3.3%)
Asthenia	2 (9.5%)	2 (2.5%)	0	1 (1.1%)	0	0
Impaired healing	0	1 (1.2%)	0	2 (2.2%)	0	1 (1.7%)
Peripheral edema/swelling	0	3 (3.7%)	1 (4.0%)	0	0	1 (1.7%)
Surgical and medical procedures						
Stent placement	0	0	0	2 (2.2%)	0	2 (3.3%)
Toe amputation	1 (4.8%)	1 (1.2%)	0	0	1 (3.4%)	0
Coronary arterial stent insertion	0	0	0	0	0	2 (3.3%)

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye						Subjects with 2 Study Eyes	
	Ranibizumab		PRP					
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89	Subjects with Baseline DME N=29	Subjects without Baseline DME N=60		
Surgery	0	0	0	0	0	0	1 (3.4%)	1 (1.7%)
Metabolism and nutrition disorders								
Dehydration	0	1 (1.2%)	1 (4.0%)	0	1 (3.4%)	0	1 (3.4%)	1 (1.7%)
Diabetic ketoacidosis	0	3 (3.7%)	1 (4.0%)	0	0	0	0	0
Fluid overload	2 (9.5%)	1 (1.2%)	0	0	0	0	0	0
Hyperglycemia	0	0	0	0	0	0	0	3 (5.0%)
Ketoacidosis	0	1 (1.2%)	0	0	0	0	1 (3.4%)	0
Cardiac disorders								
Cardiac failure congestive	2 (9.5%)	4 (4.9%)	1 (4.0%)	1 (1.1%)	0	0	0	2 (3.3%)
Myocardial infarction ^a	1 (4.8%)	1 (1.2%)	0	3 (3.4%)	0	0	0	3 (5.0%)
Coronary artery disease	1 (4.8%)	2 (2.5%)	0	0	0	0	0	0
Cardiac arrest	1 (4.8%)	1 (1.2%)	0	0	0	0	0	0
Coronary artery stenosis	1 (4.8%)	0	0	0	0	0	0	1 (1.7%)
Renal and urinary disorders								
Acute kidney injury	0	5 (6.2%)	1 (4.0%)	0	1 (3.4%)	0	1 (3.4%)	2 (3.3%)
Renal failure	3 (14.3%)	2 (2.5%)	1 (4.0%)	1 (1.1%)	0	0	0	2 (3.3%)
Chronic kidney disease	1 (4.8%)	1 (1.2%)	1 (4.0%)	1 (1.1%)	0	0	0	0
Nephropathy	2 (9.5%)	0	0	0	0	0	0	1 (1.7%)
Renal impairment	0	2 (2.5%)	0	1 (1.1%)	0	0	0	0
Nephrolithiasis	0	0	0	0	0	0	0	2 (3.3%)
Nervous system disorders								
Cerebrovascular accident	0	3 (3.7%)	2 (8.0%)	2 (2.2%)	1 (3.4%)	0	1 (3.4%)	0
Syncope	1 (4.8%)	2 (2.5%)	0	0	0	0	0	0
Hypoxic-ischemic encephalopathy	1 (4.8%)	1 (1.2%)	0	0	0	0	0	0

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye						Subjects with 2 Study Eyes	
	Ranibizumab			PRP			Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89		
Respiratory, thoracic and mediastinal disorders								
Dyspnea	4 (19.0%)	1 (1.2%)	1 (4.0%)	4 (4.5%)	0	0	2 (3.3%)	
Cough	1 (4.8%)	1 (1.2%)	0	3 (3.4%)	0	0	0	
Oropharyngeal pain	0	1 (1.2%)	0	2 (2.2%)	0	0	0	
Injury, poisoning and procedural complications								
Foot fracture	2 (9.5%)	1 (1.2%)	1 (4.0%)	0	0	0	0	
Fall	0	0	1 (4.0%)	1 (1.1%)	1 (4.0%)	1 (3.4%)	0	
Vascular disorders								
Hypertension	2 (9.5%)	2 (2.5%)	0	1 (1.1%)	0	1 (3.4%)	2 (3.3%)	
Arterial occlusive disease	0	0	0	0	0	0	2 (3.3%)	
Hypotension	0	0	0	0	0	0	2 (3.3%)	
Gastrointestinal disorders								
Vomiting	0	4 (4.9%)	2 (8.0%)	0	2 (8.0%)	1 (3.4%)	1 (1.7%)	
Nausea	0	4 (4.9%)	2 (8.0%)	0	2 (8.0%)	0	0	
Abdominal pain	0	4 (4.9%)	0	0	0	0	0	
Impaired gastric emptying	0	0	2 (8.0%)	1 (1.1%)	0	0	0	
Investigations								
Blood glucose increased	0	2 (2.5%)	0	0	0	1 (3.4%)	0	
Musculoskeletal and connective tissue disorders								
Pain in extremity	0	1 (1.2%)	0	3 (3.4%)	0	0	0	
Skin and subcutaneous tissue disorders								
Diabetic foot	0	2 (2.5%)	0	0	0	1 (3.4%)	0	

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye						Subjects with 2 Study Eyes	
	Ranibizumab		PRP		Subjects without Baseline DME N=89	Subjects with Baseline DME N=29	Subjects without Baseline DME N=60	
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89				
Skin ulcer	0	0	0	0	0	2 (6.9%)	0	
Ear and labyrinth disorders								
Vertigo	0	0	0	0	3 (3.4%)	0	0	

Source: Module 2.7.3 SCS Table 6

a Includes adverse events: myocardial infarction and acute myocardial infarction **b** Included adverse event preferred terms of cerebrovascular accident and ischemic stroke.

Serious non-ocular adverse events occurred in 44% of subjects in the ranibizumab-1 study eye subgroup without baseline DME. The most common non-ocular serious adverse events were chest pain, acute kidney injury, congestive heart failure, and pneumonia.

Common Adverse Events – Ocular and Nonocular

**Table 7.4.1-1
 Ocular Adverse Events in the Study Eye Occurring in ≥ 10% of Eyes in Any Treatment Group Through 2 Years
 Safety Evaluable Eyes**

MedDRA System Organ Class Preferred Term	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Total number of eyes with at least 1 adverse event	152 (79.6%)	36 (85.7%)	116 (77.9%)	164 (80.8%)	39 (84.4%)	125 (79.6%)
Vitreous floaters	54 (28.3%)	8 (19.0%)	46 (30.9%)	56 (27.6%)	13 (28.3%)	43 (27.4%)
Vitreous hemorrhage	39 (20.4%)	10 (23.8%)	29 (19.5%)	54 (26.6%)	10 (21.7%)	44 (28.0%)
Vision blurred	32 (16.8%)	9 (21.4%)	23 (15.4%)	54 (26.6%)	15 (32.6%)	39 (24.8%)
Visual acuity reduced	26 (13.6%)	8 (19.0%)	18 (12.1%)	38 (18.7%)	12 (26.1%)	26 (16.6%)
Eye pain	27 (14.1%)	7 (16.7%)	20 (13.4%)	30 (14.8%)	4 (8.7%)	26 (16.6%)
Dry eye	16 (8.4%)	4 (9.5%)	12 (8.1%)	15 (7.4%)	6 (13.0%)	9 (5.7%)
Visual impairment	14 (7.3%)	4 (9.5%)	10 (6.7%)	15 (7.4%)	2 (4.3%)	13 (8.3%)
Conjunctival hemorrhage	21 (11.0%)	5 (11.9%)	16 (10.7%)	7 (3.4%)	4 (8.7%)	3 (1.9%)
Cataract	10 (5.2%)	4 (9.5%)	6 (4.0%)	16 (7.9%)	4 (8.7%)	12 (7.6%)
Retinal detachment	9 (4.7%)	1 (2.4%)	8 (5.4%)	17 (8.4%)	4 (8.7%)	13 (8.3%)
Eye pruritus	12 (6.3%)	3 (7.1%)	9 (6.0%)	12 (5.9%)	3 (6.5%)	9 (5.7%)
Lacrimation increased	11 (5.8%)	4 (9.5%)	7 (4.7%)	12 (5.9%)	3 (6.5%)	9 (5.7%)
Retinal hemorrhage	13 (6.8%)	3 (7.1%)	10 (6.7%)	10 (4.9%)	2 (4.3%)	8 (5.1%)
Photopsia	8 (4.2%)	0	8 (5.4%)	13 (6.4%)	5 (10.9%)	8 (5.1%)
Eye irritation	13 (6.8%)	2 (4.8%)	11 (7.4%)	7 (3.4%)	3 (6.5%)	4 (2.5%)
Eye disorder	7 (3.7%)	1 (2.4%)	6 (4.0%)	10 (4.9%)	3 (6.5%)	7 (4.5%)
Macular fibrosis	6 (3.1%)	2 (4.8%)	4 (2.7%)	11 (5.4%)	6 (13.0%)	5 (3.2%)
Unevaluable event	21 (11.0%)	6 (14.3%)	15 (10.1%)	24 (11.8%)	9 (19.6%)	15 (9.6%)

Source: Module 2.7.3 SCS Table 6

The frequency of ocular adverse events was similar between the ranibizumab with and without baseline DME treatment groups, and between ranibizumab and PRP treatment groups.

The most common ocular adverse events in the ranibizumab without baseline DME treatment group were vitreous floaters, vitreous hemorrhage, blurred vision, eye pain, visual acuity reduced and conjunctival hemorrhage. All of these adverse events except vitreous hemorrhage are included in the Lucentis package insert.

Table 7.4.1-2
Non-Ocular Adverse Events Occurring in $\geq 10\%$ of Eyes in Any Treatment Group
Through 2 Years by Baseline DME
Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Total number of subjects with at least 1 adverse event	45 (90.0%)	128 (90.8%)	20 (80.0%)	71 (79.8%)
Infections and infestations				
Nasopharyngitis	10 (20.0%)	18 (12.8%)	3 (12.0%)	7 (7.9%)
Influenza	7 (14.0%)	13 (9.2%)	2 (8.0%)	6 (6.7%)
General disorders and administration site conditions				
Unevaluable event	3 (6.0%)	5 (3.5%)	3 (12.0%)	1 (1.1%)
Nervous system disorders				
Headache	6 (12.0%)	20 (14.2%)	3 (12.0%)	11 (12.4%)
Respiratory, thoracic and mediastinal disorders				
Cough	5 (10.0%)	19 (13.5%)	1 (4.0%)	6 (6.7%)
Dyspnea	5 (10.0%)	10 (7.1%)	1 (4.0%)	6 (6.7%)
Gastrointestinal disorders				
Nausea	5 (10.0%)	15 (10.6%)	4 (16.0%)	6 (6.7%)
Vomiting	3 (6.0%)	14 (9.9%)	3 (12.0%)	3 (3.4%)
Injury, poisoning and procedural complications				
Fall	7 (14.0%)	8 (5.7%)	3 (12.0%)	4 (4.5%)
Vascular disorders				
Hypertension	12 (24.0%)	25 (17.7%)	6 (24.0%)	14 (15.7%)
Metabolism and nutrition disorders				
Diabetes mellitus inadequate control	2 (9.5%)	10 (12.3%)	4 (16.0%)	6 (6.7%)
Renal and urinary disorders				
Nephropathy	7 (14.0%)	11 (7.8%)	2 (8.0%)	7 (7.9%)
Renal disorder	2 (4.0%)	6 (4.3%)	3 (12.0%)	2 (2.2%)
Chronic kidney disease	1 (2.0%)	4 (2.8%)	3 (12.0%)	1 (1.1%)
Cardiac disorders				
Coronary artery disease	6 (12.0%)	6 (4.3%)	0	2 (2.2%)
Psychiatric disorders				
Depression	0	2 (1.4%)	3 (12.0%)	4 (4.5%)

Source: Module 2.7.3 SCS Table 7; March 24, 2017 submission in response to Information Request #4

Ninety percent of ranibizumab subjects and eighty percent of PRP subjects experienced at least one adverse event. The rates of non-ocular adverse events were similar in ranibizumab and PRP subjects.

The most common non-ocular adverse events in ranibizumab subjects which occurred more frequently in the ranibizumab group were hypertension, nasopharyngitis, headache, influenza, nephropathy, nausea, and fall.

Antiplatelet Trialists' Collaboration Events

Antiplatelet Trialists' Collaboration events (vascular deaths, unknown cause deaths, non-fatal myocardial infarctions, non-fatal cerebrovascular accidents) were reported in 4 (19.0%) subjects in the ranibizumab- study eye subgroup with baseline DME and 6 (7.4%) subjects without baseline DME. In the 2 study eyes group, APTC events were reported in 1 (3.4%) subject with baseline DME and 5 (8.3%) subjects without baseline DME. In the PRP-1 study eye group, APTC events were reported in 2 (8.0%) subjects with baseline DME and 7 (7.9%) subjects without baseline DME.

Table 7.3.4-1 Deaths, Myocardial Infarctions, and Cerebrovascular Accidents Through 2 Years by Baseline DME Status Safety Evaluable Subjects

Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Any Event	6 (12.0%)	13 (9.2%)	4 (16.0%)	8 (9.0%)
Deaths				
Overall	4 (8.0%)	6 (4.3%)	2 (8.0%)	2 (2.2%)
Vascular	1 (2.0%)	2 (1.4%)	0	1 (1.1%)
Non-vascular	1 (2.0%)	2 (1.4%)	2 (8.0%)	1 (1.1%)
Unknown cause	2 (4.0%)	2 (1.4%)	0	0
MI or CVA				
Overall	3 (6.0%)	8 (5.7%)	2 (8.0%)	6 (6.7%)
MI				
Overall	2 (4.0%)	4 (2.8%)	0	4 (4.5%)
Fatal	0	1 (0.7%)	0	0
Non-fatal	2 (4.0%)	3 (2.1%)	0	4 (4.5%)
CVA				
Overall	1 (2.0%)	4 (2.8%)	2 (8.0%)	2 (2.2%)
Fatal	1 (2.0%)	0	0	0

Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Non-fatal	0	4 (2.8%)	2 (8.0%)	2 (2.2%)
APTC events (vascular deaths, unknown cause deaths, non-fatal MIs, non-fatal CVAs)	5 (10.0%)	11 (7.8%)	2 (8.0%)	7 (7.9%)

Note: Subjects with 2 study eyes enrolled are included in the Ranibizumab group. Subjects with 2 study eyes enrolled are considered to have baseline DME if at least 1 study eye has baseline DME.

The proportion of patients who experienced APTC events was the same for the ranibizumab (8%) and PRP (8%) treatment groups.

Safety Update

The 120-Day Safety Update was submitted on January 9, 2017. Per that submission:

For reference, BL 1215156/S-114 is based on the efficacy and safety data from a Jaeb Center for Health Research-sponsored study entitled “Prompt Panretinal Photocoagulation Versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy” (Protocol S) with a data cut off in January 2015. The first patient was enrolled in February 2012, and the study is currently ongoing with patients having been treated up to approximately 4 years.

For this safety update, Genentech reviewed the safety data of subjects without baseline diabetic macular edema (DME) in the ranibizumab arm in the ongoing Protocol S study with a data cut off of December 6, 2016. The types of ocular and non-ocular adverse events observed were consistent with the safety profile observed for this subgroup at the primary endpoint at 2 years and the well-established safety profile of Lucentis.

No additional safety information for Lucentis in patients with diabetic retinopathy (DR) without DME has become available from other clinical studies. Lucentis is currently not approved for DR patients without DME in the U.S. or outside the U.S. and no post-marketing safety data are available for this safety update.

Genentech concludes that the safety profile for the DR without baseline DME population remains favorable, and that the benefit-risk profile in this population remains unchanged. As such, no modifications to the recommended labeling submitted with BL 125156/S-114 are proposed at this time.

Safety Summary Statement

The Clinical Study Report submitted within this Supplemental BLA 125156 for Study Protocol S (Protocol ML27976) in association with the safety data which supported the previously submitted indications supports the safety of ranibizumab 0.5 mg injection in the treatment of patients with diabetic retinopathy

The most common ocular adverse events in the ranibizumab without baseline DME treatment group were vitreous floaters, vitreous hemorrhage, blurred vision, eye pain, visual acuity reduced and conjunctival hemorrhage. All of these adverse events except vitreous hemorrhage are included in the Lucentis package insert.

The most common non-ocular adverse events in ranibizumab subjects which occurred more frequently in the ranibizumab group were hypertension, nasopharyngitis, headache, influenza, nephropathy, nausea, and fall.

9. Advisory Committee Meeting

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

10. Pediatrics

The demographics of the patients enrolled in the trial during the development program for this proposed indication are representative of the targeted population.

The applicant requested and received a waiver of the pediatric study requirements for the original Biologics License Application. The FDA agreed to Genentech's request for a Pediatric Waiver (PeRC meeting held 2/8/2017). The waiver was requested because the disease under study (diabetic retinopathy) does not occur in the pediatric age group.

11. Other Relevant Regulatory Issues

DSI

A routine Division of Scientific Investigations (DSI) audit was requested. Protocol ML27976 was conducted at 57 clinical sites in the U.S. Planned enrollment was a minimum of 380 eyes with 394 eyes actually randomized to study.

Dr. Browning's site was selected for inspection because of its enrollment of a relatively large numbers of subjects.

Site #/ Name of CI Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
44/ David J. Browning, M.D., Ph.D. Charlotte Eye, Ear, Nose & Throat Associates, PA 6035 Fairview Road Charlotte, NC 28210-3256	ML27976/ 22	17-19 Jan 2017	NAI. Pending final classification.

The primary efficacy endpoint was the change in visual acuity from baseline to 2 years. This data was contained in Listing H and was confirmed for every study subject. OCT values were determined by the site and entered into the eCRFs. The OCT report was then sent to the reading center which determined its own value. Diabetic retinopathy (DR) scores were assigned by the reading center. The reading center OCT values occasionally differed from that of the site; for example:

Subject/visit/eye/ Treatment	Value on data listing/Values by Reading Center	Value in eCRF	Difference
(b) (6) baseline/L/ ranibizumab	208	215	-7
(b) (6) baseline/L/ ranibizumab	184	203	-19
(b) (6) baseline/R/ PRP	319	315	+4
(b) (6) baseline/R/ PRP	222	217	+5
(b) (6) Week 104/L/ ranibizumab	251	255	-4
(b) (6) Week 104/L/ PRP	326	347	-21
(b) (6) Week 104/R/ PRP	267	263	+4
(b) (6) Week 104/R/ PRP	149	224	-75

The data listings provided by the applicant were reportedly those values determined by the reading center. These values were not reported back to the study site. According to the study site, a review committee monitored differences in values assigned by the study site and the reading center.

Unusual differences would be investigated and additional training would be provided to the sites and/or reading center as needed. For this study, the differences in values between those determined by the study site and the reading center were not considered unusual.

A Form FDA 483 was not issued at the conclusion of the inspection. Notwithstanding the discrepant OCT results, the results of the clinical investigator inspection indicate that Dr. Browning's study conduct appears to have been adequate, and the data otherwise generated by this site appear acceptable in support of the respective indication.

CDTL Note: The applicant provided detailed responses on 3/15/2017 (SDN-901) to the Agency's information request regarding the discrepancies in OCT values. The detailed process by which central readings were handled for Protocol S was provided; the applicant's description is satisfactory. The OCT value recorded on the CRF was used for immediate DME treatment decisions and was not updated to reflect the JCHR or the Duke Reading Center OCT values. The applicant's explanation for the OCT discrepancies is acceptable.

FINANCIAL DISCLOSURE

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

From the Medical Officer Review finalized 3/29/2017:

The clinical study, Protocol S, was conducted by the Jaeb Center for Health Research (JCHR). The JCHR also held the study database and was responsible for all data management activities. Genentech was not involved in the conduct of the study, but did provide ranibizumab and funds to the JCHR to defray costs.

Of the 180 investigators that participated in Protocol S, 7 (4%) reported disclosable financial interests in Genentech. These disclosures are summarized in the table below. The number of subjects affected is 29 (9%), therefore, the potential for bias is low.

The risk of potential bias is further mitigated by the fact that the maximum number of subjects randomized at any given site was no more than 7% of the total number of subjects enrolled.

The design of Protocol S minimized the potential for bias by any investigator. By the study design, there was no single investigator or sub-investigator who had influence that could affect the results of the trial. The study was multicenter, double-blinded, randomized with an active control. The actual treatment given to individual subjects is determined by a randomization schedule.

In summary, the risk of bias for Protocol S was limited and JCHR and Genentech assessed that the financial disclosures' findings described above do not affect the integrity or reliability of the results from this study.

Clinical Site Number	Name	Subject Enrollment	Disclosure
		(b) (6)	Consultancy and lectures in total: indeterminate value ^a Board membership and lectures in total: \$69,997 Consultancy, lectures and development of educational presentations in total: \$59,997 Consultancy, lectures and travel in total: \$89,997 Consultancy and lectures in total: \$59,999 Board membership, consultancy, lectures, and travel/accommodations/meeting expenses in total: \$59,997 Board Membership, consultancy, lectures and manuscript preparation in total: \$119,997
			(b) (6)

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review for S-114 on 3/6/2017. Their comments regarding the package insert are addressed in the final labeling.

The proposed container label, carton labeling, and Prescribing Information (PI) were found acceptable from a medication error perspective.

DDMAC

The Office of Prescription Drug Promotion (OPDP) finalized a review on 3/20/17. Their comments are addressed in the final labeling.

ADL

The Associate Director for Labeling finalized a review dated 4/11/2017.

The ADL suggested removing the subheadings in Section 1 and converting the list of indications to a bulleted list. This suggestion was not incorporated since it is inconsistent with the approved labeling for products with multiple indications.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 3/24/2017:

This sBLA was based on data for which the applicant has right-of-reference from the Diabetic Retinopathy Clinical Research Network sponsored Phase 3 study (referred to as ‘Protocol S’) with a cross reference to the RISE and RIDE studies.

Protocol S was a 5-year multicenter, randomized, active-controlled study. This sBLA included all efficacy and safety data collected during the first 2 years as the study is on-going. The study enrolled a total of 305 DR subjects (394 eyes) with or without DME; 75 subjects (88 eyes) had DME in at least one eye. Randomization was stratified by baseline DME status. Subjects with a single eligible eye (N=216) were randomized in a 1:1 ratio to ranibizumab or PRP group. Subjects with two eligible eyes (n=89) received PRP in one eye and ranibizumab in the other eye randomly. Eyes in the ranibizumab group received ranibizumab 0.5 mg monthly injection for the first four injections and as needed (PRN) afterwards. Eyes in the PRP group received PRP at baseline. Eyes in both treatment groups received ranibizumab injection as needed if eyes had DME at baseline or developed DME during the study; and also received PRP treatment during the study if protocol-specified criteria were met.

In summary, ranibizumab 0.5 mg PRN in Protocol S demonstrated substantial improvement in DR severity in eyes with DR regardless of DME status.

Based on the treatment benefit of ranibizumab 0.5 mg PRN in DR patients with and without DME, the applicant requested to broaden the indication of treatment of DR regardless of DME for the approved dose of ranibizumab 0.3 mg monthly. The applicant established a bridge between the ranibizumab 0.5 mg PRN dosing regimen used in Protocol S to the approved ranibizumab 0.3 mg monthly dosing regimen based on the following considerations: (i) the consistency of results for ≥ 2 -step 2 improvement at Year 2 across doses and regimens in Protocol S and in the RISE/RIDE studies, (ii) comparable averaged amounts of ranibizumab between the 0.3 mg monthly and 0.5 mg PRN regimens over the first year for eyes without DME, (iii) similar results for monthly 0.3 mg and 0.5 mg in the RISE/RIDE studies, and (iv) similarity in disease pathology in DR patients with or without DME. The applicant's justification for a bridge between monthly 0.3 mg and 0.5 mg PRN appeared acceptable from the reviewer perspective.

The reviewer concludes that this application provides evidence of efficacy of ranibizumab 0.3 mg monthly dosing for a broad indication of treatment of DR regardless of DME status. The conclusion is based on the totality of evidence from the RIDE/RISE studies and the additional information in DR patients with and without DME provided in the Protocol S study, and the well-established safety profile of monthly ranibizumab 0.3 mg dosing and knowledge that the same dosing regimen is already approved for the treatment of DR in patients with DME.

12. Labeling

BLA 125156 for Lucentis (ranibizumab injection), Supplement 114, is recommended for approval for the treatment of patients with diabetic retinopathy (DR) with the package insert labeling submitted by Genentech, Inc., on 4/11/2017 and found in this CDTL review (see Appendix 1).

13. Recommendations/Risk Benefit Assessment

BLA 125156 for Lucentis (ranibizumab injection), Supplement 114, is recommended for approval for the treatment of patients with diabetic retinopathy (DR) with the package insert labeling submitted by Genentech, Inc., on 4/11/2017 and found in this CDTL review (see Appendix 1).

RISK BENEFIT ASSESSMENT:

The benefits of Lucentis (ranibizumab injection) for the recommended indication outweigh the associated risks.

For the Agency redefined main efficacy measure (i.e., the proportion of eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 2 years):

Eyes in the ranibizumab group experienced clinically meaningful and consistent improvements of ≥ 3 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

In the ranibizumab treatment group at the 2 year time point, the proportion of eyes with baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 32% - 40%; while the proportion of eyes without baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 28% - 35%.

For the primary efficacy variable specified in the original statistical analysis (i.e., the mean change in best corrected visual acuity from baseline in the Study Eye at 2 years):

The mean change in visual acuity from baseline in the study eye at 2 years was statistically significant in favor of the ranibizumab treatment group when compared to PRP treatment group.

The Clinical Study Report submitted within this Supplemental BLA 125156 for Study Protocol S (Protocol ML27976) in association with the safety data which supported the previously submitted indications supports the safety of ranibizumab 0.5 mg injection in the treatment of patients with diabetic retinopathy

The most common ocular adverse events in the ranibizumab without baseline DME treatment group were vitreous floaters, vitreous hemorrhage, blurred vision, eye pain, visual acuity reduced and conjunctival hemorrhage. All of these adverse events except vitreous hemorrhage are included in the Lucentis package insert.

The most common non-ocular adverse events in ranibizumab subjects which occurred more frequently in the ranibizumab group were hypertension, nasopharyngitis, headache, influenza, nephropathy, nausea, and fall.

Clinical and Biostatistics have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING ACTIONS:

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

Appendix

Attached is the package insert labeling submitted by Genentech, Inc. on 4/11/2017 and the revised 0.3 mg folding carton submitted 12/6/2016.

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

/s/

WILLIAM M BOYD
04/12/2017

WILEY A CHAMBERS
04/12/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type BLA
 Application Number(s) 125156
 Priority or Standard Priority

Submit Date(s) October 18, 2016
 Received Date(s) October 18, 2016
 PDUFA Goal Date April 18, 2017
 Division / Office DTOP / OAP

Reviewer Name(s) Rhea A. Lloyd, MD
 Review Completion Date March 29, 2017

Established Name ranibizumab injection
 (Proposed) Trade Name Lucentis
 Therapeutic Class Vascular endothelial growth factor (VEGF) inhibitor
 Applicant Genentech, Inc.
 1 DNA Way
 South San Francisco, CA 94080
 650-225-1558

Formulation(s)

Ingredients	Amount	Strength	Function	Reference to Standard or Specification
		Amount per 10 mg/mL Vial ^a		
Ranibizumab	10 mg	(b) (4) mg	Active ingredient	
α , α -trehalose dehydrate				(b) (4)
L-histidine HCl monohydrate				(b) (4)
Polysorbate 20				(b) (4)

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

Indication(s) For the treatment of diabetic retinopathy

Intended Population(s) Adults with diabetic retinopathy

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Lucentis (ranibizumab injection) is currently approved for the treatment of diabetic retinopathy in patients with diabetic macular edema. The purpose of this efficacy supplement is to demonstrate safety and efficacy in patients with diabetic retinopathy without diabetic macular edema. The findings of Protocol S not only confirm the safety and efficacy of ranibizumab in subjects with diabetic retinopathy and baseline diabetic macular edema but also, demonstrate safety and efficacy in diabetic retinopathy without baseline diabetic macular edema.

Supplement (S-114) for BLA 125156 Lucentis (ranibizumab injection) for the treatment of diabetic retinopathy is recommended for approval.

1.2 Risk Benefit Assessment

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

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.

Reference is also made to the following Supplemental BLAs for Lucentis (ranibizumab injection):

- S-053, for Lucentis (ranibizumab injection), 0.5 mg approved on June 22, 2010, for the treatment of patients with macular edema following retinal vein occlusion.
- S-076, for Lucentis (ranibizumab injection), 0.3 mg approved on August 10, 2012, for the treatment of patients with diabetic macular edema.
- S-106, for Lucentis (ranibizumab injection), 0.3 mg approved on February 6, 2015, for the treatment of diabetic retinopathy in patients with diabetic macular edema.
- S-111, for Lucentis (ranibizumab injection), 0.5 mg approved on January 5, 2017, for the treatment of myopic choroidal neovascularization.

In this supplemental BLA, Genentech seeks to update the Lucentis labeling with a new indication, the treatment of patients with diabetic retinopathy (DR).

2.2 Tables of Currently Available Treatments for Proposed Indications

Lucentis (ranibizumab injection) 0.3 mg is approved for the treatment of diabetic retinopathy in patients with diabetic macular edema.

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, the treatment of macular edema secondary to retinal vein occlusion and the treatment of myopic choroidal neovascularization.

Ranibizumab injection 0.3 mg is currently marketed by the applicant as Lucentis (ranibizumab injection) for the treatment of diabetic macular edema and for the treatment of diabetic retinopathy in patients with 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

The Jaeb Center for Health Research (JCHR) was the sponsor of Protocol S and the coordinating center for the Diabetic Research Clinical Research Network (DRCR.net). The JCHR conducted the study, and the DRCR.net supported the identification, design, and implementation of the Protocol S study. This collaboration is referred to as JCHR (DRCR.net).

Genentech did have an opportunity to review JCHR (DRCR.net)'s protocol and provide comments. However, JCHR (DRCR.net) was under no obligation to incorporate those suggestions. Genentech was not involved in the conduct of the study but did provide ranibizumab and funds to the JCHR to defray the study's costs.

September 1, 2015 – A Type B, teleconference meeting was held with Genentech to discuss a proposal to expand the diabetic retinopathy (DR) in patients with diabetic macular edema (DME) indication to include all patients with diabetic retinopathy regardless of DME status. The basis for this supplement submission was to be an analysis of retinopathy outcomes data from the Diabetic Retinopathy Clinical Research Network (DRCR.net)-sponsored study, Protocol S, which studied the treatment of DR regardless of the presence of DME using ranibizumab and panretinal photocoagulation (PRP).

At that time, the Division expressed concerns about using the data from Protocol S to support a supplemental BLA submission and suggested that the following concerns should be addressed:

- Protocol S was not designed to assess the DR endpoints as a primary endpoint or in a manner which controlled potential Type I error. An attempt to control multiplicity for endpoints used to support your submission will be post-hoc since the analyses are completed. However, an explanation should be provided regarding why the observed treatment effect for the endpoints included in your submission is not likely due to chance alone.
- In Protocol S, the comparator arm, panretinal photocoagulation, could introduce potential bias due to the inability to adequately mask the treatment groups. The impact of this potential bias on the data should be addressed.
- Ranibizumab 0.3 mg monthly is the approved dose and dosing regimen for the diabetic retinopathy with diabetic macular edema indication. Protocol S included only ranibizumab 0.5 mg dosed on a PRN dosing schedule. It is not clear how a bridge can be established from the ranibizumab 0.5 mg PRN dosing regimen to ranibizumab 0.3 mg monthly dosing regimen.
- The use of Protocol S to compare patients with diabetic retinopathy and macular edema to patients with diabetic retinopathy without macular edema has a number of limitations (e.g., post-hoc analysis, assumes treatment effect of an unapproved regimen), and has not been demonstrated in other studies. These limitations should be addressed.

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.

Progression of DR is measured in discrete steps as described by the ETDRS DR Severity Scale¹. 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

Protocol S was designed to determine the relative efficacy of ranibizumab 0.5 mg injection (0.3 mg was not yet approved) vs. panretinal photocoagulation (PRP) for the treatment of diabetic retinopathy which was the previous standard of care treatment. Because DME is a manifestation of DR, many enrolled subjects also had DME. Randomized subjects were stratified based on DME status at baseline.

Thus, Protocol S might be able to address whether ranibizumab intravitreal injections would be effective in patients with DR without DME. Demonstration of efficacy in this patient population would support broadening the indication to all patients with diabetic retinopathy.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

Dr. Browning's clinical site was inspected in support of this BLA supplement by the Office of Scientific Investigations (OSI). The classification of the inspection of Dr. Browning is No Action Indicated (NAI). See the OSI review in DARRTS dated 3/10/17.

3.2 Compliance with Good Clinical Practices

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

1 Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study Design and Baseline Patient Characteristics. *ETDRS Study Report 7. Ophthalmology* 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.

Before initiation of the study, the original protocol, all protocol amendments, the informed consent documents and all supportive information were to be reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study.

3.3 Financial Disclosures

Refer to 9.3 Clinical Investigator Financial Disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This supplemental BLA does not contain any Chemistry Manufacturing and Controls information or changes.

4.2 Clinical Microbiology

This supplemental BLA does not contain any Clinical Microbiology information or changes.

4.3 Preclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

This supplemental BLA does not contain any Clinical Pharmacology information or changes.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study	Phase	Design (Sites)	Population	No. of Subjects Enrolled	Treatment Frequency and Duration
Protocol S (Protocol ML27976)	3	Multicenter, randomized, single-masked, active treatment-controlled USA	Adult patients with proliferative diabetic retinopathy	305 subjects (394 eyes) RBZ group (n=191 eyes) PRP group (n=203 eyes)	<p>RBZ group: 0.5 mg IVT injection at randomization/baseline, 4-, 8-, and 12-week follow-up visits. Beginning at 16-week visit, eyes were evaluated for retreatment based on appearance of neovascularization.</p> <p>PRP group: A full session of 1200-1600 burns using 500 micron burns on the retina or the equivalent area treated when using indirect laser delivery systems was completed within 56 days of randomization. Study eyes in the PRP group could receive supplemental PRP if neovascularization worsened during the study following completion of the initial PRP session.</p> <p>Eyes in both groups could receive ranibizumab as needed for DME, at baseline or if DME developed during the course of the study.</p>

5.2 Review Strategy

This review evaluates the 24-month results of the Phase 3 clinical study, Protocol S.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol S: Prompt Panretinal Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

Primary Objective:

To determine if visual acuity outcomes at 2 years in eyes with proliferative diabetic retinopathy (PDR) that received 0.5 mg ranibizumab intravitreal injections with deferred panretinal photocoagulation (PRP) were non-inferior to those in eyes that received standard prompt PRP therapy.

Secondary Objectives:

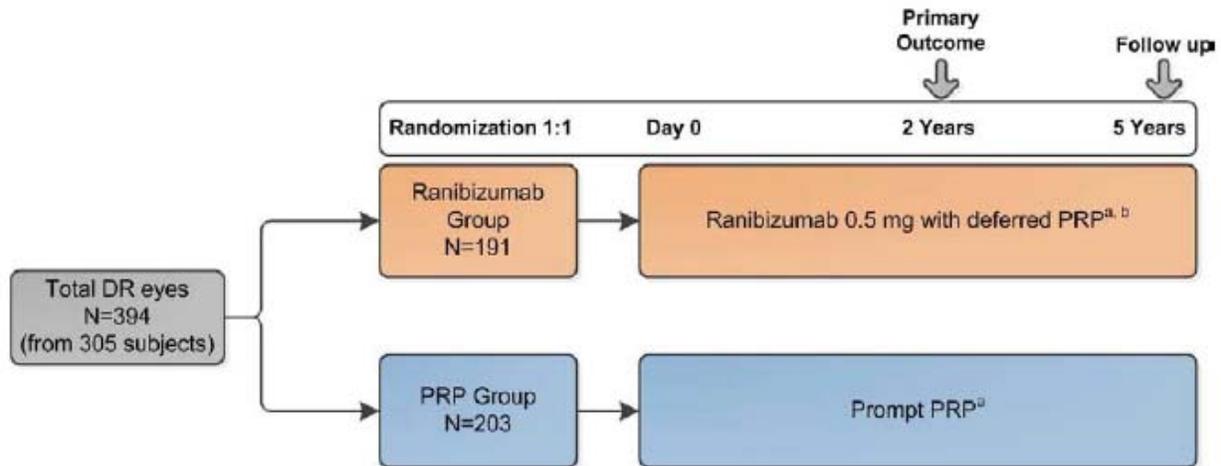
- To compare other visual function outcomes (including Humphrey visual field testing and study subject self-reports of visual function) in eyes that received ranibizumab with deferred PRP with eyes that received standard prompt PRP therapy.
- To determine the percent of eyes that did not require PRP when 0.5 mg ranibizumab intravitreal injections were given in the absence of prompt PRP.
- To compare the safety outcomes between treatment groups.
- To compare the associated treatment and follow-up examination costs between treatment groups.

JCHR (DRCR.net) was responsible for the design and conduct of the study. Protocol S was [REDACTED] (b) (4). Subsequent to the completion of the protocol, Genentech identified additional DR severity outcomes of interest which are discussed in the efficacy analysis.

Study Methodology

Protocol S study was a Phase 3, prospective, multicenter, randomized clinical trial to determine if visual acuity outcomes at 2 years in eyes with PDR that received ranibizumab with deferred PRP were non-inferior to eyes that receive standard PRP therapy.

Figure 5.3.1-1 - Overview of Study Design



DR = diabetic retinopathy; PRP = panretinal photocoagulation.

Note: Subjects could have 2 study eyes enrolled. For the visit schedule see Section 3.1 of the Protocol

^a Intravitreal ranibizumab could be given as needed for DME

^b Ranibizumab group: PRP was allowed for cases of treatment failure

The trial was designed and conducted by the JCHR (DRCR.net) at 57 clinical sites in the US. The study enrolled 305 subjects with PDR, including 89 subjects who had both eyes enrolled, for a total of 394 study eyes.

Eligible subjects were at least 18 years old with type 1 or type 2 diabetes, and had at least one study eye with PDR that had no prior PRP and in which PRP could be safely deferred for at least 4 weeks. A best corrected visual acuity (BCVA) score of at least 24 ETDRS letters (approximate Snellen equivalent of 20/320 or better) was required for all study eyes. Eyes with and without DME at baseline were eligible for inclusion in the study. Subjects provided written informed consent.

Eligible eyes were randomized to two treatment groups through the DRCRnet website. Subjects could have enrolled one or two eligible study eyes. Subjects with one study eye were randomly assigned with equal probability (stratified by site and presence of DME) to receive either PRP (hereafter referred to as the PRP group) or ranibizumab 0.5 mg intravitreal injection administered monthly through Week 12 and then less than monthly as needed (hereafter referred to as the ranibizumab group).

Treatment for Diabetic Macular Edema

If center-involved DME was present at baseline on OCT (central subfield thickness [CST] ≥ 250 microns on ZEISS Stratus or equivalent thickness on spectral domain OCT machine, within 8 days of randomization) and visual acuity was ≤ 78 (20/32 or worse), ranibizumab was given.

In all other circumstances, treatment with ranibizumab and/or focal/grid laser for DME was at investigator discretion. However, if center-involved DME was not present at baseline and developed during follow-up on OCT (central subfield thickness [CST] \geq 250 microns on ZEISS Stratus or equivalent thickness on spectral domain OCT machine) and the CST had increased from baseline at least 25 microns, it was recommended that intravitreal ranibizumab be given.

Ranibizumab Treatment

Subjects were randomized on the same day that treatment was to be initiated (i.e., Day 0). For subjects with two study eyes that were treated with ranibizumab at baseline, both eyes could be injected on the same day or on separate days as long as the second eye was injected within one week of randomization. If an eye experienced adverse effects from a prior ranibizumab injection, retreatment with ranibizumab was at the discretion of the investigator. Starting at the 16-week visit, study eyes randomized to the ranibizumab group were evaluated for retreatment intravitreal ranibizumab for PDR based on the appearance of neovascularization. Follow-up visits to evaluate for PDR retreatment were every 4 weeks in the 1st year as long as the eye had not received PRP. At and after 52 weeks or once PRP was given in the first year, if the injection for PDR was deferred at the current and previous two visits, the next study follow-up visit was in twice the time since the last visit up to a maximum of 16 weeks between visit. Otherwise, the next study follow-up visit was in 4 weeks.

PRP Treatment

In the PRP group, all study eyes received PRP which was initiated on the day of randomization for eyes without DME or initiated within 14 days of baseline if DME was present at baseline for which ranibizumab injection was indicated. If ranibizumab injection was performed on the same day, PRP was performed prior to injection. The full session of 1200 to 1600 burns using 500 micron burns on the retina or the equivalent area treated when using indirect laser delivery systems or laser (e.g., **P**Attered **S**CAnning Laser (PASCAL), which delivered an automated pattern) was completed within 56 days of randomization.

Alternative treatment (e.g., anti-VEGFs other than ranibizumab) for PDR was only permitted in this group if neovascular glaucoma had developed following completion of PRP. Otherwise, alternative treatment could only have been performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.

Ranibizumab Plus Deferred PRP Group

Eyes assigned to the ranibizumab group received PRP only if failure/futility criteria for injection for PDR were met. Failure criteria for PDR could be met starting after the first injection. If the investigator believed PRP was warranted prior to meeting failure/futility criteria for PDR, the Protocol Chair of Coordinating Center designee was contacted for approval.

Failure criteria are defined as

1. growth of NV or new NV of the retina, disc OR iris since the last visit such that the NV, including fibrosis, is greater in extent than at baseline and at least 4 study injections have been given over the previous 4 months. The investigator may perform PRP.

OR

2. New or worsened NV of the angle has developed since the last visit. The investigator may perform PRP.

OR

3. definite worsening of NV or fibrous proliferation of the retina, disc OR iris at least 1 day after the last injection that the investigator believes is likely to lead to substantial vision loss if PRP is not performed within 1 week. PRP may only be performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.

Futility criteria are defined as continued persistence or recurrence of NV at 1.5 years or later follow-up that is equal to or greater than the extent of the NV present at baseline and at least 5 study injections performed over the preceding 6 months. PRP may only be performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.

Primary Outcome

The primary outcome of this study was at 2 years; additional follow up through 5 years is ongoing. During the first 2 years, the schedule of follow-up visits depended on the treatment group assigned. However, all subjects had outcome assessment visits at 16, 32, and 52 weeks in Year 1 and 68, 84, 104 weeks in Year 2. Eyes assigned to the ranibizumab group had more frequent treatment assessment visits (every 4 to 16 weeks, through 2 years) than the PRP group (every 16 weeks).³

Study Population

The study population enrolled adult PDR patients with and without DME who fulfilled the eligibility criteria at study entry.

Inclusion Criteria

Individual-level Criteria

Patients eligible for inclusion in this study were to fulfill all of the following criteria prior to initial study drug administration:

1. Male or female patients \geq 18 years of age. Individuals $<$ 18 years old were not included because PDR is so rare in this age group that the diagnosis of PDR may be questionable.
2. Diagnosis of diabetes mellitus (Type 1 or Type 2). Any of the following were considered to be sufficient evidence that diabetes was present:
 - a. Current regular use of insulin for the treatment of diabetes
 - b. Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes

³ In the original statistical analysis, the primary efficacy variable was the mean change in visual acuity at 2 years from baseline. That data is presented in 6.1.10 Additional Efficacy Issues/ Analyses.

For this supplemental BLA submission, for the treatment of diabetic retinopathy independent of baseline DME studies, the redefined main efficacy measure: the proportion of eyes with \geq 3-step improvement from baseline in ETDRS-DRSS at 2 years. That data is presented in 6.1.4 Analysis of Diabetic Retinopathy - Main Efficacy Measure.

- c. Documented diabetes by American Diabetes Association (ADA) and/or World Health Organization (WHO) criteria
3. At least one eye met the study eye criteria below.
4. Ability and willingness to provide written informed consent.

Study Eye Criteria

The potential subject had to have had at least one eye meeting all of the inclusion criteria and none of the exclusion criteria below.

The eligibility criteria for a study eye were as follows:

1. Presence of PDR that the investigator intended to manage with PRP alone but for which PRP could be deferred for at least 4 weeks in the setting of intravitreal ranibizumab, in the investigator's judgment.
2. Best corrected Electronic- Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity letter score ≥ 24 (approximate Snellen equivalent 20/320) on the day of randomization.
3. Media clarity, pupillary dilation, and subject cooperation sufficient to administer PRP and obtain adequate fundus photographs and OCT. Investigator-verified accuracy of OCT scan by ensuring it was centered and of adequate quality.

Exclusion Criteria

Individual-Level Criteria

An individual was not eligible if any of the following exclusion criteria were present:

1. Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant
2. A condition that, in the opinion of the investigator, would have precluded participation in the study (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control)
Individuals in poor glycemic control who, within the last 4 months, initiated intensive insulin treatment (a pump or multiple daily injections) or planned to do so in the next 4 months would not have been enrolled.
3. Participation in an investigational trial within 30 days of randomization that involved treatment with any drug that had not received regulatory approval for the indication being studied.
Note: Subjects were prohibited from receiving another investigational drug while participating in the study
4. Known allergy to any component of the study drug.
5. Blood pressure $> 180/110$ (systolic above 180 or diastolic above 110)
If BP was brought below 180/110 by anti-hypertensive treatment, individual could have become eligible.
6. Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 4 months prior to randomization.

7. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization. These drugs were not to be used during the study.
8. For women of child-bearing potential: pregnant or lactating or who intended to become pregnant within the next 3 years. Women who were potential subjects were to be questioned about the potential for pregnancy. Investigator judgment was used to determine when a pregnancy test was needed.
9. Individual was expecting to move out of the area of the clinical center to an area not covered by another JCHR (DRCR.net) certified clinical center during the 3 years of the study.

Study Eye Criteria

The following exclusions applied to the study eye only (i.e., they could have been present for the non-study eye):

10. History of prior PRP (prior PRP was defined as ≥ 100 burns outside of the posterior pole)
11. Tractional retinal detachment involving the macula. A tractional retinal detachment was not an exclusion criterion if it was outside of the posterior pole (not threatening the macula) and in the investigator's judgment, was not a contraindication to intravitreal ranibizumab treatment and also did not preclude deferring PRP for at least 4 weeks in the setting of intravitreal ranibizumab.
12. Exam evidence of neovascularization of the angle (neovascularization of the iris alone was not an exclusion if it did not preclude deferring PRP for at least 4 weeks in the investigator's judgment)
13. If macular edema was present, it was considered to be primarily due to a cause other than DME.
An eye should not have been considered eligible if: (1) macular edema was present that was considered related to ocular surgery such as cataract extraction or (2) clinical exam and/or OCT suggested that vitreoretinal interface abnormalities disease (e.g., a taut posterior hyaloid or epiretinal membrane) was the primary cause of any macular edema.
14. An ocular condition was present (other than DR) that, in the opinion of the investigator might have altered visual acuity during the course of the study (e.g., retinal vein or artery occlusion, uveitis, or other ocular inflammatory, neovascular glaucoma, etc.)
A vitreous or preretinal hemorrhage was not an exclusion criterion if it was out of the visual axis and in the investigator's judgment did not have an effect on visual acuity.
15. Substantial cataract that, in the opinion of the investigator, decreased visual acuity by 3 lines or more (i.e., cataract that reduced acuity to 20/40 or worse if eye were otherwise normal).
16. History of intravitreal anti-VEGF treatment at any time in the past 2 months
17. History of corticosteroid treatment (intravitreal or peribulbar) at any time in the past 4 months. If the investigator believed that there might still have been a substantial effect 4 months after prior treatment (e.g., dose of intravitreal triamcinolone higher than 4 mg), the eye should not have been included.
18. History of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months following randomization.

19. History of yttrium aluminum garnet (YAG) capsulotomy performed within 2 months prior to randomization.
20. Aphakia
21. Uncontrolled glaucoma (in investigator's judgment)
22. Exam evidence of severe external ocular infection, including conjunctivitis, chalazion, or substantial blepharitis.

Study Treatments

PRP group: Prompt PRP
Ranibizumab group: 0.5 mg ranibizumab (intravitreal injection) with deferred PRP

Commercially available ranibizumab was used for the Protocol S study. Ranibizumab is a sterile, clear, and colorless to pale yellow, preservative-free solution aseptically filled in a sterile glass vial for single use only. Each single-dose vial was used to administer 0.05 mL from a 10 mg/mL solution (0.5 mg dose).

Commercial Ranibizumab Batch Numbers

461031, 973021, 1146868, 947864, 973021, 514406, 1146868

Treatment Masking

Subjects, investigators, and study coordinators were not masked to treatment assignments because of the nature of the treatments. The medical monitors who reviewed all AEs were masked to treatment assignments. The reading center graders, the visual acuity and OCT technicians were masked to treatment group assignments at the annual visits.

Concomitant Treatment

No systemic anti-VEGF medications or other experimental treatments were permitted. If intravitreal ranibizumab was initiated for DME, non-study anti-VEGF drugs and alternative treatments for DME (e.g., corticosteroids) were not permitted unless a minimum of 6 injections had been given and the failure criteria outlined in the protocol were met or Protocol Chair or Coordinating Center designee approval was obtained. Antibiotics in the pre-, peri-, or post-injection period were not necessary but could be used at investigator discretion if such use was part of their usual routine. Regular use of insulin and oral anti-hyperglycemia agents were permitted.

Procedure Manuals and Reading Centers

The JCHR (DRCR.net) Procedures Manuals (visual acuity-refraction testing procedures manual, photography procedures manual, OCT procedures manuals, and study-specific procedures manual) provided details of the examination procedures and intravitreal injection procedures.

Protocol-Defined Thickened OCT

- Zeiss Cirrus/ Optovue RTVue: women \geq 290 microns or men \geq 305 microns
- Heidelberg Spectralis: women \geq 305 microns or men \geq 320 microns

- Zeiss Stratus: women \geq 250 microns or men \geq 250 microns

Reading Centers

- OCT: OCT scans were obtained by certified personnel based on a standard acquisition protocol. Baseline and 2-year OCT scans were graded by the Duke Reading Center (Durham, NC)
- Fundus Photographs: 7-field or 4-Wide field images were obtained by certified personnel based on a standard acquisition protocol. If neovascularization was not identified within the standard images, additional fields were taken to confirm the neovascularization. If additional fields were obtained at baseline, they were repeated at follow-up. All images were graded by the Wisconsin Reading Center (Madison, WI)
- Visual Field: HVF testing was processed at the University of Iowa Visual Field Reading Center (Coralville, IA)

Reviewer's Comment:

The following Information Request was sent to Genentech to obtain clarification on the procedure for reading fundus photographs:

Please provide the grading instruction document used by the graders for the DRSS scale. We would like you to clarify how the DRSS score of 60 was used in grading fundus images of subjects who received PRP. Specifically, we would like to know if graders were given instruction to score diabetic retinopathy (including score below 60) despite the presence of PRP scars.

Genentech's response:

To ensure consistency, the masked graders at the University of Wisconsin Fundus Photograph Reading Center were instructed to score diabetic retinopathy (DR) severity using the DR Color Photograph Evaluation Procedures instruction document (Attachment 1). The same version of the instruction document will be used throughout the ongoing study.

As noted in the instruction document, the Diabetic Retinopathy Severity Scale (DRSS) score of 60 was used as a minimum diabetic retinopathy score where a definite presence of scars from scatter photocoagulation or panretinal photocoagulation (PRP) of any extent, including complete, partial or local scatter photocoagulation, was observed on the fundus images (Section 4.2.7.2 Scatter Photocoagulation, Appendix 2: DR Severity Scale for 7 field images and Appendix 5: DR Severity Scale for 4-wide images).

The DRSS score of 60 was assigned to fundus images with definite PRP scars, in which proliferative diabetic retinopathy (PDR) was inactive. Graders could also assign scores >60 (61 for mild PDR, 65 for moderate PDR, 71/75 for high-risk PDR, 81 or 85 for advanced PDR), if they detected presence of relevant PDR lesions in addition to the definite PRP scars.

As per established convention (Ip M. et al. Arch Ophthalmol 2012; 130:1145-1152), the images with definite PRP scars could only receive a DRSS score 60 or higher. Based on correspondence with the University of Wisconsin Fundus Photograph Reading Center, retinopathy levels below 60 were not assessed if definite PRP scars were detected.

A DRSS score below 60 could be assigned to fundus images of PRP-treated eyes if the scars observed on the fundus image could not be conclusively confirmed as resulting from scatter photocoagulation or PRP (Section 4.2.7.2 Scatter Photocoagulation, Appendix 2: DR Severity Scale for 7 field images and Appendix 5: DR Severity Scale for 4-wide images).

Thus, improvement beyond an ETDRS-DRSS score of 60 was only possible if the particular fundus photographs did not capture PRP scars. A review of the data showed that some subjects were scored with improvement lower than 60 after PRP but most were not. This grading instruction made it impossible to make an accurate relative efficacy determination between ranibizumab and PRP.

Table 5.3-1 List of Investigators

Principal Investigator Name	Center ID Number	Center Address	Number of Randomized Subjects
Melvin Chen, MD	11	Sarasota Retina Institute 3400 Bee Ridge Road, Suite 200 Sarasota, FL 34239	1
Brian B. Berger, MD	13	Retina Research Center 3705 Medical Pkwy, Suite 420 Austin, TX 78705	12
Judy E. Kim, MD	19	Medical College of Wisconsin 925 N. 87 th Street Milwaukee, WI 53226	4
Gary E. Fish, MD	21	Texas Retina Associates 9600 N. Central Expressway, Suite 100 Dallas, TX 75231	1
A. Thomas Ghuman, MD	22	National Ophthalmic Research Institute 6901 International Center Boulevard Fort Myers, FL 33912	6
Michel Shami, MD	23	Texas Retina Associates 4517 98 th Street Lubbock, TX 79424	10
Jennifer K. Sun, MD	39	Joslin Diabetes Center Beetham Eye Institute One Joslin Place Boston, MA 02215	4
Stewart A. Daniels, MD	41	Bay Area Retina Associates 122 LaCasa Via, Suite 223 Walnut Creek, CA 94598	3

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Principal Investigator Name	Center ID Number	Center Address	Number of Randomized Subjects
David Browning, MD, PhD	44	Charlotte Eye, Ear, Nose and Throat Associates, PA 6035 Fairview Road Charlotte, NC 28210	22
Mathew W. MacCumber, MD, PhD	45	Rush University Medical Center Department of Ophthalmology 1725 W. Harrison Street, Suite 931 Chicago, IL 60612	1
Raj K. Maturi, MD	46	Raj K. Maturi, MD, PC 200 West 103 rd Street, Suite 1060 Indianapolis, IN 46290	4
James L. Kinyoun, MD	47	University of Washington Medical Center 325 9 th Ave., Box 359608 Seattle, WA 98104	3
Joseph M. Googe, Jr., MD	48	Southeastern Retina Associates 1124 Weisgarber Road, Suite 207 Knoxville, TN 37909	4
Joseph A. Khawly, MD	49	Retina and Vitreous of Texas 2727 Gramercy St., Suite 200 Houston, TX 77025	2
Sharon D. Solomon, MD	53	Wilmer Eye Institute at Johns Hopkins 600 North Wolfe Street Maumenee 215, Second Floor Baltimore, MD 21287	1
Michael A. Novak, MD	55	Retina Associates of Cleveland, Inc. 3401 Enterprise Parkway, Suite 300 Beachwood, OH 44122	5
Dante J. Pieramici, MD	67	California Retina Consultants 525 E. Micheltorena St., Suites A & D Santa Barbara, CA 93103-4223	12
Carl W. Baker, MD	69	Paducah Retinal Center 4630 Village Square Dr., Suite 201 Paducah, KY 42001	14
G. Robert Hampton, MD	72	Retina-Vitreous Surgeons of Central New York, PC 3107 E. Genesee Street Syracuse, NY 13224	4
Alexander J. Brucker, MD	76	University of Pennsylvania Scheie Eye Institute 51 N. 39 th Street, Scheie 616 Philadelphia, PA 19104	2
David M. Brown, MD, FACS	80	Retina Consultants of Houston, PA 6560 Fannin St., Suite 750 Houston, TX 77030	6

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Principal Investigator Name	Center ID Number	Center Address	Number of Randomized Subjects
Ronald C. Gentile, MD	86	The New York Eye and Ear Infirmary Faculty Eye Practice Ophthalmology Clinical Research Department 310 East 14 th Street, Suite 319 South New York, NY	1
Hugo Quiroz-Mercado, MD	88	Denver Health Medical Center 777 Bannock Street Denver, CO 80204	4
Andreas K. Lauer, MD	89	Casey Eye Institute 3375 Terwilliger Boulevard Portland, OR 97239	6
Jeffrey G. Gross, MD	90	Carolina Retina Institute 7620 Trenholm Road Extension Columbia, SC 29223	10
Joseph T. Fan, MD	91	Loma Linda University Health Care Department of Ophthalmology Faculty Medical Offices 11370 Anderson St., Suite 1800 Loma Linda, CA 92354	7
Scott M. Friedman, MD	100	Florida Retina Consultants 2202 Lakeland Hills Blvd Lakeland FL 33805	12
David Allen DiLoreto, Jr., MD, PhD	106	University of Rochester 601 Elmwood Ave, Rm G-3020 Flaum Eye Institute Rochester, NY 14642	3
Mark A. Peters, MD, FACS	109	Retina Northwest, PC 2525 NW Lovejoy, Suite 300 Portland, OR 97210	9
Michael J. Elman, MD	111	Elman Retina Group, PA 9114 Philadelphia Road, Suite 310 Baltimore, MD 21237	17
Kevin J. Blinder, MD	118	The Retina Institute 12348 Old Tesson Road, Suite 280 St. Louis, MO 63128	1
Victor Hugo Gonzalez, MD	127	Valley Retina Institute 1309 E. Ridge Rd., Suite 1 McAllen, TX 78503	10
Thomas W. Stone, MD	129	Retina and Vitreous Associates of Kentucky 12 North Eagle Creek Drive, Suite 500 Lexington, KY 40509	0*
Clement K. Chan, MD, FACS	133	Southern California Desert Retina Consultants, MC 36949 Cook Street, Suite 101 Palm Desert, CA 92211	1

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Principal Investigator Name	Center ID Number	Center Address	Number of Randomized Subjects
Dennis M. Marcus, MD	152	Southeast Retina Center, P.C. 3685 Wheeler Road, Suite 201 Augusta, GA 30909	13
Michael Pavlica, MD	156	Family Eye Group 2110 Harrisburg Pike, Suite 215 Lancaster, PA 17601	4
Brett T. Foxman, MD	158	Retinal and Ophthalmic Consultants, PC 1500 Tilton Road Northfield, NJ 08255	3
Kakarla V. Chalam, MD, PhD, MBA, FACS	163	University of Florida College of Med. Department of Ophthalmology Jacksonville Health Science 580 W. 8 th Street Jacksonville, FL 32290	4
Gregory M. Haffner, MD	180	New England Retina Associates 400 Bayonet St., Suite 206 New London, CT 06320	10
Calvin E. Mein, MD	193	Retinal Consultants of San Antonio 9480 Huebner Road, Suite 310 San Antonio, TX 78240	9
Petros Euthymiou Carvounis, MD	194	Baylor Eye Physicians and Surgeons Baylor College of Medicine 1977 Butler Blvd., Suite E3 153 Houston, TX 77030	2
Karl R. Olsen, MD	208	Retina Vitreous Consultants 300 Oxford Drive, Suite 300 Monroeville, PA 15146	2
Karim N. Jamal, MD	212	Retinal Consultants of Arizona 1101 E. Missouri Ave. Phoenix, AZ 85014	1
Darren J. Bell, MD	216	Medical Center Ophthalmology Assoc. 9157 Huebner Road San Antonio, TX 78240	4
Jared S. Nielsen, MD	221	Wolfe Eye Clinic 6200 Westown Pkwy. West Des Moines, IA 50266	4
Umar Khalil Mian, MD	231	Montefiore Medical Center 3400 Bainbridge Ave. Bronx, NY 10467	1
Chander N. Samy, MD	232	Ocala Eye Retina Consultants 3130 SW 32 nd Avenue Ocala, FL 34474	5
Manvi P. Maker, MD	235	North Shore University Health System 2050 Pfingsten Road, Suite 280 Glenview, IL 60026	1

Clinical Review
Rhea A. Lloyd, MD
BLA 125156 / S-114
Lucentis (ranibizumab injection) 0.3 mg

Principal Investigator Name	Center ID Number	Center Address	Number of Randomized Subjects
Thomas W. Gardner, MD, MS	239	Kellogg Eye Center University of Michigan 1000 Wall Street Ann Arbor, MI 48105	5
Robin D. Ross, MD	243	Retina Vitreous Center 3181 E. Grand Blanc Rd. Grand Blanc, MI 48439-2709	4
Thomas M. Aaberg, Jr, MD	244	Retina Specialists of Michigan 5030 Cascade Road, SE Suite 200 Grand Rapids, MI 49546	4
Stuart K. Burgess, MD	249	Fort Lauderdale Eye Institute 850 S. Pine Island Road, Suite A100 Plantation, FL 33324	10
Robert W. Wong, MD	250	Austin Retina Associates 801 W. 38 th Street, Suite 200 Austin, TX 78705-1169	3
Frank J. McCabe, MD	252	Vitreoretinal Associates, PC 67 Belmont Street, Suite 302 Worcester, MA 01605	8
Robert S. Wirthlin, MD	253	Spokane Eye Clinic 427 South Bernard Street Spokane, WA 99204	3
Amr Dessouki, MD	255	Retinal Diagnostic Center 3395 S. Bascom Ave., Suite 140 Campbell, CA 95008	1
Ivan J. Suner, MD	261	Retinal Associates of Florida, PA 602 South MacDill Avenue Tampa, FL 33609	2

Schedule of Assessment Visits and Examination Procedures

	0	Treatment Visits Every 4–16w ^a (± 1w)	Non-Annual Assessment Visits ^b (±2 to 4w)	Annual Visits (± 4w)
Visit Window				
E-ETDRS best corrected visual acuity ^c	X	X	X	X
Binocular visual acuity ^d	X			X
Ancillary visual field testing ^e	X			X
Questionnaires ^f	X		X	X
OCT ^g	X	X		X
Eye Exam ^h	X	X	X	X
Fundus Photography ⁱ	X			X
Blood pressure	X			
HbA _{1c} ^j	X			

DME = diabetic macular edema; E-ETDRS = Electronic-Early Treatment Diabetic Retinopathy Study; HbA_{1c} = glycosylated hemoglobin; HVF = Humphrey visual field; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; NVI = neovascularization of the iris; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; TTO = Time Trade-Off Questionnaire; UAB-LLQ = UAB Low Luminance Questionnaire; WPAI = Workplace Productivity and Activity Impairment Questionnaire.

^a Visits every 4 weeks (w) during the first year for eyes assigned to ranibizumab with deferred PRP; if intravitreal ranibizumab treatment was initiated for DME in either group, additional visits for DME treatment occurred every 4 to 16 weeks as needed. After 1 year from initial ranibizumab treatment for PDR or once PRP was given, visits were scheduled every 4-16 weeks based on disease progression and treatment administered.

^b Visits at 16 (±2), 32 (±2), 68 (±4), 84 (±4), 120 (±4), and 136 (±4). For subjects who agreed to structured follow-up in Years 4 and 5, additional assessment visits at 172 (±4), 188 (±4), 224 (±4), and 240 (±4) weeks.

^c Both eyes including protocol refraction in the study eye at each visit. Protocol refraction in non-study eye was only required at baseline and annual visits. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester that was validated against 4-meter chart ETDRS testing.

^d Binocular vision test using habitual correction on the Electronic Visual Acuity Tester.

Schedule of Assessment Visits and Examination Procedures (Continued)

- ^e Humphrey visual field testing (30-2 and 60-4 test patterns; at sites with HVF testing capabilities).
- ^f Only in subjects with one study eye; included NEI-VFQ-25, UAB-LLQ, and TTO annually only; WPAI at 4w and each subsequent assessment visit.
- ^g Study eye only at annual visits for all eyes and at each follow-up visit for eyes in which DME treatment was initiated.
- ^h Both eyes at baseline; study eye only at each follow-up visit including slit lamp exam, lens assessment, measurement of intraocular pressure, and dilated ophthalmoscopy; examination of the angle required if NVI or increased intraocular pressure present.
- ⁱ Study eye only at baseline, annual visits AND prior to initiating PRP in the deferred group; 7SF or 4WF with additional fields as necessary to capture presence of neovascularization
- ^j Did not need to be repeated if HbA_{1c} was available from within the prior 3 months. If was not available, could have been performed within 3 weeks after randomization.

Analysis Methods

Background

Protocol S was designed and conducted by JCHR (DRCR.net). The results published by the DRCR.net (Diabetic Retinopathy Clinical Research Network et al. 2015) are supported by the JCHR (DRCR.net) SAP. The primary endpoint (mean visual acuity change at 2 years; 5-letter non-inferiority margin; intent-to-treat [ITT] population) as designed by the JCHR (DRCR.net) protocol was met and described in the DRCR.net publication (Diabetic Retinopathy Clinical Research Network et al. 2015).

Genentech developed a SAP for the Protocol S study after database lock for the primary efficacy endpoint, and therefore Genentech had no input on the study hypothesis or sample size estimate. Genentech's SAP describes the analysis of the Protocol S study efficacy and safety data used to support approval for the use of ranibizumab in the treatment of DR independent of DME status. Genentech's SAP describes the analysis methods used to analyze the pre-specified endpoints from the JCHR (DRCR.net) protocol and additional efficacy and safety outcome measures evaluated by Genentech, which were not identified in the JCHR (DRCR.net) protocol. In addition, there was no strict Type I error management plan for the proposed analyses of the Protocol S study data to support approval for the use of ranibizumab in the treatment of DR independent of DME status. The Genentech SAP is described in this section.

Statistical Analysis Plan for the Diabetic Retinopathy Indication Independent of DME Status

Genentech identified independent of JCHR (DRCR.net), the following additional efficacy outcome measures to support approval for the use of ranibizumab in the treatment of DR independent of DME status. The following binary variables compared treatment groups using the CMH χ^2 test (Landis et al. 1978) stratified by baseline DME status, and number of study eyes enrolled.

Main Efficacy Measure:

- Proportion of eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 1 year and at 2 years (Primary)

Supportive Efficacy Measures:

- Proportion of eyes with ≥ 2 -step improvement from baseline in ETDRS-DRSS at 1 year and at 2 years
- Proportion of eyes with ≥ 3 -step worsening from baseline in ETDRS-DRSS at 1 year and at 2 years
- Proportion of eyes with ≥ 2 -step improvement from baseline in ETDRS-DRSS from PDR at baseline to NPDR at 1 year or 2 years

For the endpoints identified in the study protocol and the additional efficacy endpoints involving change from baseline at 2 years, the change from baseline was summarized at the annual visits. At the annual visits, the change from baseline was compared using the t-test from the ANOVA

or ANCOVA model for continuous variables and using the CMH χ^2 test for binary variables, including the same baseline strata previously defined for the 2-year time point.

Sensitivity and subgroup analyses, respectively, were performed for the BCVA and ETDRS-DRSS step change (as assessed on fundus photography) endpoints.

Sample Size

The sample size was calculated to be 177 eyes in each group. This was increased to 190 eyes per group (380 total eyes) to account for loss to follow-up. Assuming 20% of subjects have two study eyes (based on enrollment in previous JCHR (DCRC.net) studies, this equates with having approximately 316 subjects.

Analysis Populations

Randomized Eyes (ITT Population):

The ITT population included all eyes randomized in the Protocol S study, whether treatment was received or not. Treatment groups for this population were defined according to the treatment assignment at randomization.

The analysis population for the change from baseline in BCVA, OCT, and ETDRS-DRSS endpoints (as assessed on color fundus photography) consisted of randomized eyes with a valid score at baseline. The analysis population for the HVF testing endpoint consisted of randomized eyes with a valid score at baseline from sites with HVF capabilities. Assessments of binocular visual acuity and questionnaires included subjects with one study eye enrolled with a valid score at baseline.

Safety-Evaluable Eyes

The population for safety-evaluable eyes included randomized eyes that received at least one study treatment (ranibizumab or PRP). Treatment groups for this population were defined according to the actual treatment received or if an eye received both study treatments, the treatment group was as randomized.

Safety-Evaluable Subject

The population for safety-evaluable subjects included randomized subjects that received at least one study treatment (ranibizumab or PRP). Treatment groups for this population were defined separately for subjects with one and two study eyes enrolled, according to the actual treatment received during the 2-year period up to and including the 2-year visit.

The treatment group for subjects who received treatment in one study eye was defined as:

- If a subject received only one active treatment (ranibizumab or PRP), the treatment group for this subject was that of the active treatment received.
- If a subject received both study treatments (ranibizumab and PRP), the treatment group for this subject was as randomized.

The treatment group for subjects who received treatment in two study eyes was defined as:

- If a subject received only one active treatment (ranibizumab or PRP), the treatment group for this subject was that of the active treatment received.
- If a subject received both study treatments (ranibizumab and PRP), the treatment group for this subject was bilateral treatment.

Efficacy Analysis

Efficacy endpoint analyses included data from randomization up to the 2-year (Week 104) visit. Analyses of the efficacy endpoints included all randomized eyes (the ITT population) unless specified otherwise. Eyes were analyzed according to their randomized treatment assignment. Missing data were imputed using the last observation carried forward (LOCF) method for the efficacy analyses unless specified otherwise.

Sensitivity Analyses

The following sensitivity analyses (identified by Genentech, independent of JCHR [DRCR.net]) were performed to support the mean change from baseline in BCVA at 2 years and ETDRS-DRSS step change endpoints at 2 years.

The following analyses were performed to assess the robustness of the results with regard to different methods of handling missing data. The analysis methods were as specified for these endpoints.

- Analyses based on observed data: the observed data was a subset of randomized eyes that had non-missing scores at both baseline and Year 2.
- Analyses based on randomized eyes, with missing data imputed using Markov Chain Monte Carlo (MCMC) multiple imputation.

Subgroup Analyses

Subgroup analyses were performed for the BCVA endpoint (mean change from baseline in BCVA at 2 years). Subgroup analyses included in the study protocol were performed by categories of the following demographic and baseline variables:

- Baseline DME status
- Baseline BCVA (<79 letters vs. ≥ 79 letters)
- Baseline OCT (OCT CST <250 VS. OCT CST ≥ 250)
- Prior DME treatment history (yes vs. no)
- Baseline ETDRS-DRSS score (< level 71 vs. \geq level 71)
- Sex
- Race (White vs Black or African American vs. other)
- Individual sites with at least 20 subjects enrolled

The following additional subgroup analyses, identified by Genentech, were also included for the endpoint of mean change from baseline in BCVA score:

- Age (<65 vs. ≥ 65 years)
- Number of study eyes enrolled (one eye vs. two eyes)

Genentech also provided subgroup analyses for the ETDRS-DRSS step change endpoint for each of the subgroups (baseline DME status, baseline BCVA, baseline OCT, prior DME treatment, baseline ETDRSS-DRSS score, sex, race, individual sites with at least 20 subjects enrolled, age, and number of study eyes enrolled) defined above.

Pharmacodynamic and Pharmacokinetic Data Analysis

Pharmacokinetic data was not collected during this study; there are no planned pharmacokinetic efficacy outcome measures.

Safety Reporting and Analysis

Safety was assessed through the summary of ocular and non-ocular AEs, serious adverse events (SAEs), ocular and non-ocular AEs of special interest (AESI) as well as selected non-ocular AEs consistent with the Antiplatelet Trialists' Collaboration (APTC) classifications, and death. Safety analyses included the safety-evaluable eyes for ocular analyses and a safety-evaluable subjects for non-ocular analyses. The safety populations were analyzed according to the actual treatment received as defined.

Safety Summaries for the 2-year analysis included all data from randomization up to the 2-year (Week 104) visit or the early termination visit for subjects who discontinued early from the study prior to 2 years. For subjects who remained in the study after 2 years but missed the year 2 visit, all data with an AE onset date between randomization and 756 days (104 + 4 weeks) from randomization was included in the 2-year analysis.

Interim Analyses

No formal efficacy interim analyses were planned as described in the DSMC monitoring plan.

Changes in the Conduct of the Study or Planned Analyses

The protocol Version 1 was finalized on October 6, 2011. The protocol (see Version 2) was amended after enrollment of the first subject and finalized on October 28, 2014. The purpose of this amendment was to extend the treatment schedule to 5 years to collect longer term data in safety and efficacy measures.

Genentech developed a SAP that describes the analysis of the Protocol S study efficacy and safety data used to support the approval of ranibizumab in the treatment of DR independent of DME status. Genentech's SAP describes the analysis methods used to analyze the pre-specified endpoints from the JCHR (DRCR.net) protocol and additional efficacy and safety outcome measures evaluated by Genentech, which were not identified in the JCHR (DRCR.net) protocol. In addition, there was no strict Type I error management plan for the proposed analyses of the Protocol S study data.

6 Review of Efficacy

Efficacy Summary

Reviewer's Comment:

The fundus photograph grading instructions given to the reading center stated that if prior panretinal photocoagulation scars were visible on fundus photograph, it should be given a score of '60' and diabetic retinopathy would not otherwise be evaluated. Thus, for the majority of subjects in the PRP treatment group improvements in diabetic retinopathy after initial PRP treatment were not captured. Improvement beyond an ETDRS-DRSS score of 60 was only possible if the particular fundus photographs did not capture PRP scars. A review of the data showed that some subjects were scored with improvement lower than 60 after PRP but most were not. Thus, making a relative efficacy determination between the ranibizumab and PRP treatment groups was not possible.

Additionally, fifty-four percent of subjects randomized to the PRP treatment group also received ranibizumab injections through the 2 year time point. This high rate of ranibizumab treatment in PRP treatment group makes it problematic to draw any conclusions regarding the relative safety and efficacy of these two treatments.

While the patients treated with PRP are not able to contribute information about the efficacy of ranibizumab, patients without PRP are still able to provide information regarding the treatment of diabetic retinopathy in subjects with and without baseline diabetic macular edema.

6.1 Indication

This supplemental BLA presents information to support revision of the Lucentis package insert to include the treatment of diabetic retinopathy (DR) independent of baseline diabetic macular edema (DME).

The 24-month data from Protocol S was submitted on October 18, 2016, in support of the safety and efficacy of Lucentis (ranibizumab injection) for the treatment of diabetic retinopathy.

6.1.1 Methods

The 2 Year (Week 104) data from Protocol S was submitted in this supplemental BLA which is reviewed here for safety and efficacy.

6.1.2 Demographics

**Table 6.1.2-1 Baseline Demographics and Characteristics
Randomized Eyes**

Demographic variable	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Age (yr)						
n	191	42	149	203	46	157
Mean (SD)	50.4 (11.5)	52.7 (9.2)	49.8 (12.0)	50.5 (11.7)	53.2 (11.4)	49.1 (11.7)
Median	51.0	54.0	50.0	51.0	55.5	49.0
Min – Max	20 – 79	27 – 68	20 – 79	22 – 83	23 – 83	22 – 83
Age group (yr)						
n	191	42	149	203	46	157
< 65	173 (90.6)	40 (95.2)	133 (89.3)	187 (92.1)	42 (91.3)	145 (92.4)
≥ 65	18 (9.4)	2 (4.8)	16 (10.7)	16 (7.9)	4 (8.7)	12 (7.6)
Min – Max	20 – 79	27 – 68	20 – 79	22 – 83	23 – 83	22 – 83
Sex						
n	191	42	149	203	46	157
Male	108 (56.5)	27 (64.3)	81 (54.4)	111 (54.7)	23 (50.0)	88 (56.1)
Female	83 (43.5)	15 (35.7)	68 (45.6)	92 (45.3)	23 (50.0)	69 (43.9)
Number of eyes enrolled						
n	191	42	149	203	46	157
One study eye	102 (53.4)	21 (50.0)	81 (54.4)	114 (56.2)	25 (54.3)	89 (56.7)
Two study eyes	89 (46.6)	21 (50.0)	68 (45.6)	89 (43.8)	21 (45.7)	68 (43.3)

Demographic variable	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Ethnicity						
n	191	42	149	203	46	157
Hispanic or Latino	48 (25.1)	13 (31.0)	35 (23.5)	51 (25.1)	9 (19.6)	42 (26.8)
Not Hispanic or Latino	136 (71.2)	24 (57.1)	112 (75.2)	144 (70.9)	35 (76.1)	109 (69.4)
Unknown / not reported	7 (3.7)	5 (11.9)	2 (1.3)	8 (3.9)	2 (4.3)	6 (3.8)
Race						
n	191	42	149	203	46	157
American Indian or Alaska Native	1 (0.5)	0	1 (0.7)	0	0	0
Asian	2 (1.0)	0	2 (1.3)	3 (1.5)	1 (2.2)	2 (1.3)
Black or African American	40 (20.9)	8 (19.0)	32 (21.5)	43 (21.2)	6 (13.0)	37 (23.6)
White	135 (70.7)	32 (76.2)	103 (69.1)	143 (70.4)	38 (82.6)	105 (66.9)
More than one race	1 (0.5)	1 (2.4)	0	2 (1.0)	0	2 (1.3)
Unknown / not reported	12 (6.3)	1 (2.4)	11 (7.4)	12 (5.9)	1 (2.2)	11 (7.0)
Duration of Diabetes at Randomization (yr)						
n	191	42	149	203	46	157
Type 1	43 (22.5)	5 (11.9)	38 (25.5)	41 (20.2)	8 (17.4)	33 (21.0)
Type 2	140 (73.3)	34 (81.0)	106 (71.1)	155 (76.4)	34 (73.9)	121 (77.1)
Uncertain	8 (4.2)	3 (7.1)	5 (3.4)	7 (3.4)	4 (8.7)	3 (1.9)
Insulin Use						
n	191	42	149	203	46	157
Yes	135 (70.7)	28 (66.7)	107 (71.8)	149 (73.4)	27 (58.7)	122 (77.7)
No	56 (29.3)	14 (33.3)	42 (28.2)	54 (26.6)	19 (41.3)	35 (22.3)
Glycosylated Hemoglobin (HbA1c)						

Demographic variable	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
n	184	41	143	498	46	152
Mean (SD)	9.02 (2.27)	9.03 (2.66)	9.02 (2.15)	9.10 (2.16)	8.65 (2.27)	9.23 (2.12)
Median	8.60	8.00	8.60	8.85	7.80	9.05
Min – Max	4.8 – 17.3	5.7 – 17.3	4.8 – 16.2	4.8 – 17.3	5.7 – 17.3	4.8 – 15.6
Baseline Systolic BP (mmHg)						
n	191	42	149	203	46	157
Mean (SD)	134.5 (19.9)	139.8 (24.7)	133.0 (18.2)	134.7 (18.9)	136.0 (19.6)	134.2 (18.7)
Median	135.0	143.5	132.0	135.0	140.0	133.0
Min – Max	85 – 180	85 – 180	100 -178	83 – 177	89 – 170	83 – 177
Baseline Diastolic BP (mmHg)						
n	191	42	149	203	46	157
Mean (SD)	80.3 (11.0)	81.7 (12.9)	79.9 (10.4)	80.0 (11.7)	80.1 (12.4)	80.0 (11.5)
Median	81.0	85.5	80.0	80.0	80.0	81.0
Min – Max	52 – 108	55 – 106	52 – 108	46 – 108	46 – 105	50 – 108

Source: SCE Table 2

Reviewer’s Comment:

The proportion of subjects in either treatment group without baseline DME to those with baseline DME was approximately 3 to 1.

The mean age ranged was approximately 50 years with a range of 20 – 79 years in the ranibizumab group. The overall duration of diabetes at randomization was a mean of 18 years. Seventy to eighty percent of subjects in the ranibizumab group had Type 2 diabetes. The mean hemoglobin A1C was 9 in the ranibizumab group.

Ranibizumab treatment group demographics with and without baseline DME were comparable.

**Table 6.1.2-2 Baseline Ocular Characteristics by Baseline DME Status
Randomized Eyes**

Ocular Characteristic	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Study eye						
n	191	42	149	203	46	157
Right eye	94 (49.2)	19 (45.2)	75 (50.3)	98 (48.3)	21 (45.7)	77 (49.0)
Left eye	97 (50.8)	23 (54.8)	74 (49.7)	105 (51.7)	25 (54.3)	80 (51.0)
Visual acuity, number of letters (0-100)						
n	191	42	149	203	46	157
Mean (SD)	75.0 (12.8)	63.8 (14.1)	78.1 (10.5)	75.2 (12.5)	64.7 (13.0)	78.3 (10.5)
Median	77.0	68.5	80.0	78.0	69.5	81.0
Min – Max	25 – 97	25 – 78	32 – 97	26 – 96	26 – 78	41 – 96
Visual acuity, method						
n	191	42	149	203	46	157
EVA-ETDRS	191 (100.0)	42 (100.0)	149 (100.0)	203 (100.0)	46 (100.0)	157 (100.0)
Visual acuity, approximate Snellen equivalent						
n	191	42	149	203	46	157
Worse than 20/200	5 (2.6)	4 (9.5)	1 (0.7)	2 (1.0)	2 (4.3)	0
Better than 20/40 and worse than 20/200	35 (18.3)	17 (40.5)	18 (12.1)	41 (20.2)	17 (37.0)	24 (15.3)
20/40 or better	151 (79.1)	21 (50.0)	130 (87.2)	160 (78.8)	27 (58.7)	133 (84.7)
Intraocular pressure (mmHg)						
n	191	42	149	203	46	157

Ocular Characteristic	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Mean (SD)	15.1 (3.0)	15.0 (3.1)	15.2 (3.1)	15.0 (3.4)	14.9 (3.0)	15.1 (3.5)
Median	15.0	15.0	15.0	15.0	15.0	15.0
Min – Max	8 – 24	9 – 22	8 – 24	7 – 23	8 – 20	7 – 23
Intraocular pressure method						
n	191	42	149	203	46	157
Tonopen	80 (41.9)	16 (38.1)	64 (43.0)	84 (41.4)	19 (41.3)	65 (41.4)
Goldmann	108 (56.5)	24 (57.1)	84 (56.4)	117 (57.6)	27 (58.7)	90 (57.3)
Other	3 (1.6)	2 (4.8)	1 (0.7)	2 (1.0)	0	2 (1.3)
Central subfield thickness (mcm)						
n	189	42	147	201	46	155
Mean (SD)	308.0 (108.5)	458.1 (126.8)	265.1 (48.1)	295.5 (85.9)	393.2 (123.6)	266.5 (37.6)
Median	276.0	436.5	261.0	277.0	336.5	268.0
Min – Max	165 – 779	256 – 779	165 – 584	153 – 857	250 – 857	153 – 370
OCT Machine						
n	189	42	147	201	46	155
Zeiss Cirrus	89 (47.1)	16 (38.1)	73 (49.7)	95 (47.3)	20 (43.5)	75 (48.4)
Zeiss Stratus	18 (9.5)	7 (16.7)	11 (7.5)	17 (8.5)	7 (15.2)	10 (6.5)
Heidelberg Spectralis	79 (41.8)	17 (40.5)	62 (42.2)	87 (43.3)	19 (41.3)	68 (43.9)
Optovue RTVue	3 (1.6)	2 (4.8)	1 (0.7)	2 (1.0)	0	2 (1.3)
CI-DME regardless of visual acuity						
n	191	42	149	203	46	157
Present	55 (28.8)	42 (100.0)	13 (8.7)	62 (30.5)	46 (100.0)	16 (10.2)
Absent	136 (71.2)	0	136 (91.3)	141 (69.5)	0	141 (89.8)

Ocular Characteristic	Ranibizumab 0.5 mg				PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)	
Neovascularization on clinical examination							
Neovascularization of the disc	191	42	149	203	46	157	
Yes	96 (50.3)	29 (69.0)	67 (45.0)	103 (50.7)	28 (60.9)	75 (47.8)	
No	93 (48.7)	13 (31.0)	80 (53.7)	100 (49.3)	18 (39.1)	82 (52.2)	
Cannot determine	2 (1.0)	0	2 (1.3)	0	0	0	
Neovascularization elsewhere	191	42	149	203	46	157	
Yes	166 (86.9)	33 (78.6)	133 (89.3)	174 (85.7)	37 (80.4)	137 (87.3)	
No	21 (11.0)	6 (14.3)	15 (10.1)	25 (12.3)	8 (17.4)	17 (10.8)	
Cannot determine	4 (2.1)	3 (7.1)	1 (0.7)	4 (2.0)	1 (2.2)	3 (1.9)	
Neovascular glaucoma							
n	191	42	149	203	46	157	
Absent	191 (100.0)	42 (100.0)	149 (100.0)	203 (100.0)	46 (100.0)	157 (100.0)	
Lens status, clinical examination							
n	191	42	149	203	46	157	
Phakic	170 (89.0)	35 (83.3)	135 (90.6)	187 (92.1)	42 (91.3)	145 (92.4)	
PCIOL	21 (11.0)	7 (16.7)	14 (9.4)	16 (7.9)	4 (8.7)	12 (7.6)	
Lens Opacity							
n	191	42	149	203	46	157	
None	60 (31.4)	16 (38.1)	44 (29.5)	64 (31.5)	11 (23.9)	53 (33.8)	
Minimal, no effect on visual acuity	126 (66.0)	26 (61.9)	100 (67.1)	134 (66.0)	33 (71.7)	101 (64.3)	
Visually significant	5 (2.6)	0	5 (3.4)	5 (2.5)	2 (4.3)	3 (1.9)	
Fundus Photography Fields							
n	191	42	149	201	46	155	

	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Ocular Characteristic						
7 fields	141 (73.8)	31 (73.8)	110 (73.8)	149 (74.1)	34 (73.9)	115 (74.2)
4-wide filed (digital only)	50 (26.2)	11 (26.2)	39 (26.2)	52 (25.9)	12 (26.1)	40 (25.8)

Source: CSR Summary of Clinical Efficacy, Table 3

Reviewer’s Comment:

Baseline visual acuity was better in the groups without baseline DME as would be expected. Thirteen subjects in the ranibizumab group without baseline DME did have DME as assessed by the investigator. Of the subjects in the ranibizumab treatment group with baseline DME, approximately 45% had NVD, 90% had NVE and none had neovascular glaucoma.

Table 6.1.2-3
Baseline ETDRS Diabetic Retinopathy Severity Score by Baseline DME Status
Randomized Eyes

Baseline Diabetic Retinopathy Severity Score	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
14A – 14C, 14Z, 15, 20 (DR questionnaire, microaneurysms only)	0	0	0	1 (0.5)	1 (2.2)	0
35A – 35F (mild NPDR)	6 (3.1)	0	6 (4.0)	4 (2.0)	0	4 (2.5)
43A, 43B (moderate NPDR)	2 (1.0)	1 (2.4)	1 (0.7)	5 (2.5)	2 (4.3)	3 (1.9)
47A – 47D (moderately severe NPDR)	10 (5.2)	2 (4.8)	8 (5.4)	15 (7.4)	1 (2.2)	14 (8.9)
53A – 53E (severe NPDR)	1 (0.5)	0	1 (0.7)	1 (0.5)	1 (2.2)	0
60 (prior PRP; without active PDR)	0	0	0	1 (0.5)	0	1 (0.6)
61A, 61B (mild PDR)	30 (15.7)	5 (11.9)	25 (16.8)	31 (15.3)	6 (13.0)	25 (15.9)
65A – 65C (moderate PDR)	68 (35.6)	12 (28.6)	56 (37.6)	67 (33.0)	15 (32.6)	52 (33.1)
71A – 71D (high-risk PDR)	47 (24.6)	13 (31.0)	34 (22.8)	53 (26.1)	15 (32.6)	38 (24.2)
75 (high-risk PDR)	22 (11.5)	8 (19.0)	14 (9.4)	20 (9.9)	4 (8.7)	16 (10.2)
81 (advanced PDR, macula center attached)	2 (1.0)	0	2 (1.3)	0	0	0
85 (advanced PDR, macula center detached)	1 (0.5)	0	1 (0.7)	1 (0.5)	0	1 (0.6)
90 (missing or cannot grade)	2 (1.0)	1 (2.4)	1 (0.7)	4 (2.0)	1 (2.2)	3 (1.9)

Source: CSR Summary of Clinical Efficacy, Table 4.

Reviewer’s Comment: *The majority of subjects had PDR, Baseline ETDRS Diabetic Retinopathy Severity Scale scores (61A-71D) in all treatment group regardless of baseline DME. Baseline ETDRS Diabetic Retinopathy Severity Scale scores were balanced across the treatment groups.*

Table 6.1.2-3
Targeted Medical History and Baseline Conditions by Baseline DME Status
Safety Evaluable Subjects

Diagnosis	Subjects with 1 Study Eye				Subjects with 2 Study Eyes ^a	
	Ranibizumab 0.5 mg		PRP		Eyes with Baseline DME	Eyes without Baseline DME
	Eyes with Baseline DME N=21 n (%)	Eyes without Baseline DME N=81 n (%)	Eyes with Baseline DME N=25 n (%)	Eyes without Baseline DME N=89 n (%)	N=29 n (%)	N=60 n (%)
Cardiac Disorders	3 (14.3)	11 (13.6)	2 (8.0)	14 (15.7)	5 (17.2)	11 (18.3)
Angina pectoris	0	0	0	2 (2.2)	0	1 (1.7)
Arrhythmia	0	1 (1.2)	0	1 (1.1)	1 (3.4)	0
Arteriosclerosis, coronary artery	0	1 (1.2)	0	0	0	2 (3.3)
Atrial fibrillation	0	0	0	0	0	1 (1.7)
Cardiac failure	1 (4.8)	2 (2.5)	0	0	0	1 (1.7)
Congestive cardiac failure	2 (9.5)	4 (4.9)	1 (4.0)	3 (3.4)	1 (3.4)	2 (3.3)
Coronary artery disease	1 (4.8)	3 (3.7)	1 (4.0)	8 (9.0)	0	3 (5.0)
Hypertensive heart disease	0	0	0	0	2 (6.9)	3 (5.0)
In-stent coronary artery re-stenosis	0	0	0	1 (1.1)	0	0
Myocardial infarction	1 (4.8)	1 (1.2)	0	3 (3.4)	0	1 (1.7)
Tachycardia	0	2 (2.5)	0	0	2 (6.9)	0
Endocrine disorders	21 (100.0)	81 (100.0)	25 (100.0)	88 (98.9)	29 (100.0)	60 (100.0)
Diabetes mellitus	21 (100.0)	79 (97.5)	25 (100.0)	87 (97.8)	29 (100.0)	57 (95.0)
Diabetes mellitus inadequate control	0	2 (2.5)	1 (4.0)	1 (1.1)	0	3 (5.0)
Eye disorders	0	5 (6.2)	0	3 (3.4)	1 (3.4)	3 (5.0)
Angle closure glaucoma	0	1 (1.2)	0	0	0	0

Diagnosis	Subjects with 1 Study Eye						Subjects with 2 Study Eyes ^a	
	Ranibizumab 0.5 mg			PRP			Eyes with Baseline DME N=29 n (%)	Eyes without Baseline DME N=60 n (%)
	Eyes with Baseline DME N=21 n (%)	Eyes without Baseline DME N=81 n (%)	Eyes with Baseline DME N=25 n (%)	Eyes without Baseline DME N=89 n (%)				
Borderline glaucoma	0	1 (1.2)	0	0	0	1 (3.4)	1 (1.7)	
Glaucoma	0	3 (3.7)	0	3 (3.4)	1 (3.4)	2 (3.3)	0	
Infections and infestations	1 (4.8)	1 (1.2)	0	1 (1.1)	0	0	0	
Diverticulitis	1 (4.8)	1 (1.2)	0	1 (1.1)	0	0	0	
Investigations	1 (4.8)	0	0	1 (1.1)	0	0	0	
Heart rate irregular	1 (4.8)	0	0	0	0	0	0	
Protein urine present	0	0	0	1 (1.1)	0	0	0	
Musculoskeletal and connective tissue disorders	0	2 (2.5)	2 (8.0)	5 (5.6)	0	2 (3.3)	0	
Rheumatoid arthritis	0	2 (2.5)	2 (8.0)	5 (5.6)	0	2 (3.3)	0	
Renal and urinary disorders	2 (9.5)	4 (4.9)	1 (4.0)	2 (2.2)	0	2 (3.3)	0	
Microalbuminuria	0	1 (1.2)	0	0	0	1 (1.7)	0	
Proteinuria	0	0	0	1 (1.1)	0	0	0	
Renal failure	0	1 (1.2)	1 (4.0)	1 (1.1)	0	1 (1.7)	0	
Chronic renal failure	2 (9.5)	2 (2.5)	0	0	0	0	0	
Skin and subcutaneous tissue disorders	0	1 (1.2)	0	0	0	1 (1.7)	0	
Allergic dermatitis	0	1 (1.2)	0	0	0	1 (1.7)	0	
Surgical and medical procedures	1 (4.8)	0	0	1 (1.1)	0	1 (1.7)	0	
Arterial bypass operation	1 (4.8)	0	0	0	0	0	0	
Coronary arterial stent insertion	0	0	0	1 (1.1)	0	1 (1.7)	0	
Coronary artery bypass	0	0	0	1 (1.1)	0	0	0	
Vascular disorders	15 (71.4)	59 (72.8)	18 (72.0)	68 (76.4)	17 (58.6)	38 (63.3)	0	

Diagnosis	Subjects with 1 Study Eye				Subjects with 2 Study Eyes ^a	
	Ranibizumab 0.5 mg		PRP		Eyes with Baseline DME N=29 n (%)	Eyes without Baseline DME N=60 n (%)
	Eyes with Baseline DME N=21 n (%)	Eyes without Baseline DME N=81 n (%)	Eyes with Baseline DME N=25 n (%)	Eyes without Baseline DME N=89 n (%)		
Cerebrovascular accident	0	1 (1.2)	0	1 (1.1)	2 (6.9)	0
Hypertension	15 (71.4)	58 (71.6)	18 (72.0)	68 (76.4)	17 (58.6)	38 (63.3)
Ischemic stroke	0	1 (1.2)	0	0	0	0
Transient ischemic attack	0	2 (2.5)	0	0	0	0

Source: CSR Summary of Clinical Efficacy, Table 4.

^a Subjects with 2 study eyes enrolled are considered to have baseline DME if at least 1 study eye has baseline DME. Cell entries are the number (%) of subjects with a known history for that diagnosis, whether or not the condition was currently active at screening.

Reviewer’s Comment: *All subjects had past medical history significant for diabetes mellitus and 59-72% for hypertension.*

6.1.3 Subject Disposition

Three hundred and thirty-seven subjects were screened and 394 study eyes from 305 subjects with diabetic retinopathy were enrolled and randomized. Overall 57 investigational sites in the United States participated in the study. Thirty-two subjects signed informed consent forms but failed screening and were not randomized to the study. A total of 89 subjects had two study eyes enrolled; one eye randomized to the ranibizumab group and the other randomized to the PRP group. All randomized eyes received at least one treatment.

Table 6.1.3-1
Subject Disposition and Primary Reason for Discontinuation Through 2 Years
by Baseline DME Status: Randomized Eyes

Status / Primary Reason for Discontinuation	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Randomized	191 (100.0)	---	---	203 (100.0)	---	---
Safety evaluable eyes ^a	191	---	---	203	---	---
Safety evaluable subjects ^c	102	---	---	114	---	---
Eyes completing study through 1 year	181 (94.8)	39 (92.9)	142 (95.3)	192 (94.6)	43 (93.5)	149 (94.9)
Eyes completing study through 2 years	163 (85.3)	33 (78.6)	130 (87.2)	176 (86.7)	39 (84.8)	137 (87.3)
Eyes discontinued from study prior to 2 years	28 (14.7)	9 (21.4)	19 (12.8)	27 (13.3)	7 (15.2)	20 (12.7)
Death ^b	10 (5.2)	4 (9.5)	6 (4.0)	8 (3.9)	3 (6.5)	5 (3.2)
Lost to follow up	10 (5.2)	1 (2.4)	9 (6.0)	11 (5.4)	2 (4.3)	9 (5.7)
Site withdrew subject	2 (1.0)	1 (2.4)	1 (0.7)	3 (1.5)	0	3 (1.9)
Subject formally withdrew consent (in writing)	1 (0.9)	0	1 (0.7)	0	0	0
Subject formally withdrew consent (not in writing)	5 (2.6)	3 (1.7)	2 (1.3)	5 (2.5)	2 (4.3)	3 (1.9)

Source: SCE Table 1; CSR Protocol S, Table 4

Note: **a** Eyes are considered to have completed the study through 2 years if the Week 104 visit was completed, or if discontinuation from the study occurred > 756 days from randomization (104 weeks + 4 weeks, per protocol visit schedule); **b** Includes 4 deaths in subjects with 2 study eyes (there were a total of 14 deaths through 2 years of the study); **c** 89 subjects had 2 study eyes.

Reviewer’s Comment: *Eighty-seven percent of subjects without DME completed the study through 2 years in both the ranibizumab and PRP groups. Thirteen percent of subjects without DME discontinued prior to 2 years. The most common reasons for discontinuation were ‘death’ and ‘lost to follow-up’.*

Table 6.1.3-2 Concurrent Ocular Procedures Through 2 Years by Baseline DME Status Randomized Eyes

Ocular Procedure	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Any Concurrent Ocular Procedure	34 (17.8)	15 (35.7)	19 (12.8)	61 (30.0)	20 (43.5)	41 (26.1)
Anterior chamber tap	0	0	0	1 (0.5)	0	1 (0.6)
Avastin injection (not for DME)	0	0	0	5 (2.5)	2 (4.3)	3 (1.9)
Cataract extraction with IOL placement	4 (2.1)	1 (2.4)	3 (2.0)	11 (5.4)	2 (4.3)	9 (5.7)
Cataract extraction without IOL placement	0	0	0	1 (0.5)	1 (2.2)	0
Endolaser	1 (0.5)	1 (2.4)	0	0	0	0
Focal/grid laser (for DME)	15 (7.9)	8 (19.0)	7 (4.7)	22 (10.8)	10 (21.7)	12 (7.6)
Focal/grid laser (non-center involved DME)	1 (0.5)	1 (2.4)	0	1 (0.5)	1 (2.2)	0
Glaucoma filter (with tube)	0	0	0	1 (0.5)	1 (2.2)	0
Intravitreal injection – antibiotics	1 (0.5)	0	1 (0.7)	0	0	0
Intravitreal ranibizumab injection for CME	1 (0.5)	1 (2.4)	0	0	0	0
Iridectomy	1 (0.5)	0	1 (0.7)	1 (0.5)	0	1 (0.6)
Laser retinopexy	1 (0.5)	0	1 (0.7)	0	0	0
Laser iridotomy	0	0	0	1 (0.5)	0	1 (0.6)
Paracentesis	3 (1.6)	1 (2.4)	2 (1.3)	2 (1.0)	2 (4.3)	0
Retinal cryopexy	0	0	0	1 (0.5)	0	1 (0.6)
Retinal detachment repair – injection of air/gas	1 (0.5)	1 (2.4)	0	1 (0.5)	1 (2.2)	0

Ocular Procedure	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Retinal detachment repair – surgical	0	0	0	1 (0.5)	1 (2.2)	0
Scleral buckle	0	0	0	1 (0.5)	0	1 (0.6)
Silicone oil injection	0	0	0	1 (0.5)	1 (2.2)	0
Silicone oil removal	0	0	0	1 (0.5)	0	1 (0.6)
Subtenons Kenalog injection of uveitis	0	0	0	1 (0.5)	0	1 (0.6)
Total air-fluid exchange	0	0	0	1 (0.5)	0	1 (0.6)
Vitrectomy	2 (1.0)	1 (2.4)	1 (0.7)	9 (4.4)	3 (6.5)	6 (3.8)
Vitrectomy with epiretinal membrane peel	1 (0.5)	1 (2.4)	0	6 (3.0)	1 (2.2)	5 (3.2)
Ahmed valve (neovascular glaucoma)	1 (0.5)	0	1 (0.7)	0	0	0
Blepharoplasty	1 (0.5)	0	1 (0.7)	1 (0.5)	0	1 (0.6)
Conjunctival cyst removal	1 (0.5)	0	1 (0.7)	0	0	0
Diode laser (open angle glaucoma)	0	0	0	1 (0.5)	1 (2.2)	0
Intravitreal bevacizumab injection for vitreous hemorrhage	1 (0.5)	1 (2.4)	0	3 (1.5)	1 (2.2)	2 (1.3)
Intravitreal ranibizumab injection for vitreous hemorrhage	0	0	0	1 (0.5)	1 (2.2)	0
Vitrectomy with endolaser	5 (2.6)	3 (7.1)	2 (1.3)	15 (7.4)	4 (8.7)	11 (7.0)

Reviewer’s comment:

Concurrent ocular procedures through 2 years were performed three times more often in the eyes with baseline DME ranibizumab subgroup compared with eyes without baseline DME ranibizumab subgroup. Focal/grid laser for DME was the most common concurrent ocular procedure performed in eyes both treatment groups.

6.1.4 Analysis of Diabetic Retinopathy - Main Efficacy Measure

In the original statistical analysis, the primary efficacy variable was the mean change in visual acuity at 2 years from baseline. That data is presented in 6.1.10 Additional Efficacy Issues/Analyses.

For this supplemental BLA submission for the treatment of diabetic retinopathy independent of baseline DME studies, the redefined main efficacy measure is: the proportion of eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 2 years.

Table 6.1.4-1
Proportion of Eyes with ≥ 3 -Step Improvement from Baseline in Ranibizumab Group in ETDRS-DRSS by Baseline DME Status
(Eyes with a Valid ETDRS-DRSS at Baseline)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
AT 1 YEAR		
LOCF		
N	41	148
n (%)	13 (31.7%)	41 (27.7%)
95% CI for percentage	(17.5%, 46.0%)	(20.5%, 34.9%)
Difference in percentages		4.0%
95% CI for difference		(-12.0%, 20.0%)
Observed		
N	33	122
n (%)	13 (39.4%)	41 (33.6%)
95% CI for percentage	(22.7%, 56.1%)	(25.2%, 42.0%)
Difference in percentages		5.8%
95% CI for difference		(-12.9%, 24.4%)
Multiple Imputation		
N	41	148
n (%)	16 (40.6%)	54 (36.8%)
95% CI for percentage	(23.8%, 57.4%)	(28.4%, 45.1%)
Difference in percentages		3.9%
95% CI for difference		(-15.3%, 23.0%)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
AT 2 YEARS		
LOCF		
N	41	148
n (%)	13 (31.7%)	41 (28.4%)
95% CI for percentage	(17.5%, 46.0%)	(21.1%, 35.6%)
Difference in percentages		3.3%
95% CI for difference		(-12.7%, 19.3%)
Observed		
N	27	116
n (%)	10 (37.0%)	38 (32.8%)
95% CI for percentage	(18.8%, 55.3%)	(24.2%, 41.3%)
Difference in percentages		4.3%
95% CI for difference		(-15.8%, 24.4%)
Multiple Imputation		
N	41	148
n (%)	16 (40.2%)	51 (35.1%)
95% CI for percentage	(22.9%, 57.6%)	(26.9%, 43.4%)
Difference in percentages		5.1%
95% CI for difference		(-13.8%, 24.0%)

Source: Module 2.7.3 SCE Table 9 and 10; Response to IR #4 dated March 24, 2017.

Note: ICs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputation, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 3 -step improvement.

Reviewer’s Comment:

Eyes in the ranibizumab group experienced clinically meaningful and consistent improvements of ≥ 3 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

In the ranibizumab treatment group at the 2 year time point, the proportion of eyes with baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 32% - 40%; while the proportion of eyes without baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 28% - 35%.

Sensitivity Analysis

Table 6.1.4-2
Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement from Baseline in ETRDS-DRSS:
Ranibizumab Groups with versus without DME at Baseline in Phase 3 Studies

Protocol S ^a	≥ 2 -Step Improvement			≥ 3 -Step Improvement		
	0.5 mg RBZ PRN No DME % (n/N) 95% CI	DME % (n/N) 95% CI	Difference (95% CI)	0.5 mg RBZ PRN No DME % (n/N) 95% CI	DME % (n/N) 95% CI	Difference (95% CI)
Week 104	37.8 (56/148) (30.0, 45.7)	58.5 (24/41) (43.5, 73.6)	20.7 (3.7, 37.7)	28.4 (42/148) (21.1, 35.6)	31.7 (13/41) (17.5, 46.0)	3.3 (-12.7, 19.3)
Study FVF4168g – RIDE^{b, c}	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)
Month 24	4.0 (5/124) (0.6, 7.5)	36.1 (43/119) (27.5, 44.8)	32.0 (22.8, 41.2)	2.4 (3/124) (0.0, 5.1)	17.6 (21/119) (10.8, 24.5)	15.0 (7.8, 22.2)
Study FVF4170g – RISE^{b, c}	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)	Sham % (n/N) 95% CI	0.5 mg RBZ % (n/N) 95% CI	Difference (95% CI)
Month 24	7.0 (8/115) (2.3, 11.6)	35.7 (41/115) (26.9, 44.4)	28.3 (18.9, 37.7)	0 (0/0) (0.0, 0.0)	11.3 (13/115) (5.5, 17.1)	11.7 (5.9, 17.4)

^a S-114, Response to IR #4 dated March 24, 2017. CIs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputation, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 3 -step improvement. LOCF

^b Source: S-106 Module 5.3.5.3 ISE Tables 12 and 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 ($\leq 8\%$, $> 8\%$), and prior therapy for DME in the study eye (yes, no). 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.

Reviewer's Comment:

At 2 years, the treatment group difference of 0.5 mg ranibizumab monthly compared to sham treatment was 28 – 32% in the RIDE study for the proportion of patients who experienced a \geq 2-step improvement from baseline in ETDRS-DRSS and 12 - 15% in the RISE study for the proportion of patients who experienced a \geq 3-step improvement from baseline in ETDRS-DRSS.

The lower bound of the confidence intervals of the differences in RIDE and RISE studies for the proportion of patients who experienced a \geq 2-step improvement from baseline in ETDRS-DRSS were 19 – 23%. The lower bound of the confidence intervals of the differences in RIDE and RISE studies for the proportion of patients who experienced a \geq 3-step improvement from baseline in ETDRS-DRSS were 6 – 8%.

At 2 years in Protocol S, the 0.5 mg ranibizumab PRN treatment group differences for patients without DME compared to those with DME was 21% for the proportion of patients who experienced a \geq 2-step improvement from baseline in ETDRS-DRSS and 3% in the for the proportion of patients who experienced a \geq 3-step improvement from baseline in ETDRS-DRSS. These findings demonstrate a comparable treatment effect and no significant difference between patients with and without DME.

6.1.5 New Supportive Endpoint Analyses

Table 6.1.5-1
Proportion of Eyes with ≥ 2 -Step Improvement from Baseline in Ranibizumab Group in ETDRS-DRSS by Baseline DME Status (Eyes with a Valid ETDRS-DRSS at Baseline)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
AT 1 YEAR		
LOCF		
N	41	148
n (%)	20 (48.8%)	59 (39.9%)
95% CI for percentage	(33.5%, 64.1%)	(32.0%, 47.8%)
Difference in percentages		8.9%
95% CI for difference		(-8.3%, 26.1%)
Observed		
N	33	122
n (%)	20 (60.6%)	59 (48.4%)
95% CI for percentage	(43.9%, 77.3%)	(39.5%, 57.2%)
Difference in percentages		12.2%
95% CI for difference		(-6.6%, 31.1%)
Multiple Imputation		
N	41	148
n (%)	25 (61.1%)	76 (51.7%)
95% CI for percentage	(44.7%, 77.5%)	(43.2%, 60.2%)
Difference in percentages		9.4%
95% CI for difference		(-9.0%, 27.8%)
AT 2 YEARS		
LOCF		
N	41	148
n (%)	24 (58.5%)	56 (37.8%)
95% CI for percentage	(43.4%, 73.6%)	(30.0%, 45.7%)
Difference in percentages		20.7%
95% CI for difference		(3.7%, 37.7%)

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
Observed		
N	27	116
n (%)	18 (66.7%)	49 (42.2%)
95% CI for percentage	(48.9%, 84.4%)	(33.3%, 51.2%)
Difference in percentages		24.4%
95% CI for difference		(4.5%, 44.3%)
Multiple Imputation		
N	41	148
n (%)	27 (66.3%)	68 (46.2%)
95% CI for percentage	(49.4%, 83.3%)	(37.5%, 54.9%)
Difference in percentages		20.1%
95% CI for difference		(0.6%, 39.6%)

Source: Module 2.7.3 SCE Table 9 and 10; Response to IR #4 dated March 24, 2017.

Note: ICs for percentages and differences in percentages are based on normal approximation for binomial proportions. For multiple imputations, the estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 3 -step improvement.

Reviewer’s Comment:

Eyes in the ranibizumab group experienced clinically meaningful and consistent improvements of ≥ 2 -step improvements from baseline in the ETDRS-DRSS independent of baseline DME status at 1 year and at 2 year time points regardless of baseline DME status.

In the ranibizumab treatment group at the 2 year time point, the proportion of eyes with baseline DME that experienced a ≥ 2 -step improvement from baseline in the ETDRS-DRSS ranged from 59% - 67%; while the proportion of eyes without baseline DME that experienced a ≥ 3 -step improvement from baseline in the ETDRS-DRSS ranged from 38% - 46%.

Sensitivity Analysis

**Table 6.1.5-2
Proportion of Eyes with Improvement of \geq 2-Step in ETDRS-DRSS
from PDR at Baseline to NPDR at 1 Year and 2 Years by Baseline DME Status
(Eyes with PDR and a Valid ETDRS-DRSS at Baseline; LOCF)**

	Ranibizumab 0.5 mg	
	Eyes with Baseline DME	Eyes without Baseline DME
1 Year (Week 52)		
N	38	132
n (%)	10 (26.3%)	38 (28.8%)
95% CI for percentage ^a	(12.3%, 40.3%)	(21.1%, 36.5%)
Difference in percentages		-2.5%
95% CI for difference ^a		(-18.5%, 13.5%)
2 Years (Week 104)		
N	38	132
n (%)	9 (23.7%)	37 (28.0%)
95% CI for percentage ^a	(10.2%, 37.2%)	(20.4%, 35.7%)
Difference in percentages		-4.3%
95% CI for difference ^a		(-19.9%, 11.2%)

Source: S-114, Response to IR #4 dated March 24, 2017.

PDR is defined as an ETDRS-DRSS score \geq 60; NPDR is defined as an ETDRS-DRSS score $<$ 60.

^a CIs for percentages and differences in percentages are based on normal approximation for binomial proportions.

Reviewer’s Comment:

There was no significant difference in the proportion of eyes with \geq 2-step improvement in ETDRS-DRSS from PDR at Baseline to NPDR at 1 Year and 2 Years by baseline DME status.

A similar proportion of patients in the ranibizumab treated group with and without DME experienced and improvement of in ETDRS-DRSS from PDR at baseline to NPDR.

Table 6.1.5-3
Proportion of Eyes with ≥ 3 -Step Worsening from Baseline in ETDRS-DRSS at 1 Year and 2 Years by Baseline DME Status
(Eyes with a Valid ETDRS-DRSS at Baseline; LOCF)

	Ranibizumab 0.5 mg		
	Overall	Eyes with Baseline DME	Eyes without Baseline DME
≥ 3-step worsening at 1 year			
N	189	41	148
n (%)	1 (0.5%)	0	1 (0.7%)
95% CI for percentage	(0.0%, 1.6%)	---	(0.0%, 2.0%)
≥ 3-step worsening at 2 years			
N	189	41	148
n (%)	4 (2.1%)	0	4 (2.7%)
95% CI for percentage	(0.1%, 4.2%)	---	(0.1%, 5.3%)
≥ 2-step worsening at 1 year			
N	189	41	148
n (%)	3 (1.6%)	1 (2.4%)	2 (1.4%)
95% CI for percentage	(0.0%, 3.4%)	(0.0%, 7.2%)	(0.0%, 3.2%)
			1.1%
			(-4.0%, 6.2%)
≥ 2-step worsening at 2 years			
N	189	41	148
n (%)	7 (3.7%)	0	7 (4.7%)
95% CI for percentage	(1.0%, 6.4%)	---	(1.3%, 8.1%)
			-4.7%
			(-8.1%, -1.3%)

Source: Module 2.7.3 SCE Table 13 and 14

a The estimated count for responders within each treatment group is based on the estimated MI proportion multiplied by the sample size. Fractions of eyes are rounded down for ≥ 2 -step improvement.

Reviewer's comment: *Few patients experienced a ≥ 2 -step worsening from baseline in ETDRS-DRSS in the ranibizumab group independent of baseline DME at 1 year and 2 year time points.*

6.1.6 Other Endpoints

No additional endpoints were required to establish the efficacy of the drug product.

6.1.7 Subpopulations

Subgroup analyses were conducted for the proportion of the eyes with ≥ 3 -step improvement from baseline in ETDRS-DRSS at 1 and 2 years by baseline DME status for the age, sex, race and baseline ETDRS-DRSS.

The number of patients within the subgroup with baseline DME was small making it difficult to draw definitive conclusions regarding safety and efficacy. There do not appear to have been any race or ethnicity effects.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Genentech proposes to make the currently approved regimen for treatment of DME and DR in patients with DME, 0.3 mg monthly, available for treatment of DR in patients without DME.

DME and DR are clinical manifestations of the same microvascular pathology and represent a spectrum of diabetic eye disease. VEGF is one of the key factors mediating the underlying pathology in all diabetic eye disease patients with or without DME. DME is a complication of DR that can occur at any stage of DR. While clinically significant DME occurs primarily in the central macula, the VEGF mediated pathology associated with DR is observed across the entire retina.

The benefit on DR severity (measured by anatomic changes across the retina, not just DME) of the 0.3 mg and 0.5 mg monthly doses in DME patients was essentially the same in Studies FVF4168g and FVF4170g. It is likewise anticipated that these doses would similarly have a consistent effect in DR patients without DME. The evidence presented in the current submission suggests that DR patients will experience comparable benefits on DR severity endpoints in response to both 0.3 mg monthly and 0.5 mg PRN ranibizumab treatment in DR eyes independent of DME presence at baseline. The further rationale for that statement is as follows:

- Studies FVF4168g and FVF4170g, which were submitted in support of the treatment of DME and DR in patients with DME indications, demonstrated that 0.3 mg and 0.5 mg ranibizumab dosed monthly have a comparable effect on DR severity endpoints at multiple time points up to 36 months in DR patients with DME.
- In Protocol S, DR eyes with DME demonstrated that 0.5 mg ranibizumab dosed monthly for 3 months and then PRN was effective in improving DR severity endpoints at 1 and 2 year time points.

- Protocol S also demonstrated that 0.5 mg ranibizumab dosed monthly for 3 months and then PRN was effective in treating DR severity in a clinically meaningful proportion of DR eyes without baseline DME, including the main endpoint of the proportion of eyes with a ≥ 3 -step improvement from baseline in ETDRS-DRSS at the 1 and 2 year time points,.

Reviewer's Comment:

Lucentis (ranibizumab injection) 0.3-mg dose has been demonstrated to be safe and effective in two Phase 3 clinical trials for the treatment of diabetic retinopathy in patients with diabetic macular edema. In all Phase 3 trials submitted for Lucentis (ranibizumab injection), the 0.3-mg and 0.5 mg doses demonstrated essentially the same efficacy and were at the top of the dose efficacy curves. The safety profile of the 0.3-mg monthly dosing regimen has been well established in diabetic patients since the approvals of Supplement 076 for the treatment of patients with diabetic macular edema in August 2012 and of Supplement 106 for the treatment of diabetic retinopathy in patients with diabetic macular edema in February 2015.

The proposed dose selection of 0.3-mg monthly is acceptable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There has been no evidence of persistence of efficacy and/or tolerance effects with Lucentis.

6.1.10 Additional Efficacy Issues/Analyses

In the original statistical analysis, the primary efficacy variable was the mean change in best corrected visual acuity from baseline in the Study Eye at 2 years.

Primary Efficacy Results – Original Statistical Analysis Plan

Table 6.1.10-1
Mean Change in Best Corrected Visual Acuity (ETDRS letters) from Baseline
in the Study Eye at 2 Years (LOCF) Randomized Eyes

	Ranibizumab 0.5 mg N=191	PRP Total N=203
Baseline		
n	191	203
Mean (SD)	75.0 (12.8)	75.2 (12.5)
Median	77.0	78.0
Min – Max	0.0- 12.0	-4.0 – 7.0
Week 104 (2 Years)		
n	191	203
Mean (SD)	2.7 (17.8)	-0.7 (15.5)
Median (SE)	5.0 (1.3)	1.0 (1.1)
95% CI for mean	(0.2, 5.2)	(-2.8, 1.5)
Difference in means		3.4
95% CI for difference		(0.1, 6.6)
Test for Treatment Difference		
Student t-test (unstratified)		0.0460
ANOVA t-test (stratified)		0.0382

Source: Module 5.3.5.1 CSR ML27976 Section 5.2.1 Table 16

Stratification variables in stratified analyses: baseline DME status and number of eyes enrolled. All CIs are 2-sided. CIs for means and differences in means are based on Student t-distribution (Unstratified). Estimates and CIs for LS means and differences in LS means are from the ANOVA model (stratified).

Reviewer’s comment: *The study met the primary efficacy endpoint as pre-specified in the original statistical analysis plan. The mean change in visual acuity from baseline in the study eye at 2 years was statistically significant in favor of the ranibizumab treatment group when compared to PRP treatment group.*

7 Review of Safety

Safety Summary

This safety summary focuses on the ranibizumab without DME subgroup. There were approximately three times as many subjects without DME as with DME at baseline, therefore, direct group comparisons are problematic. Also, 54% of subjects in the PRP treatment groups received ranibizumab injections during the study thus confounding treatment group comparisons as well.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review of safety describes the safety profile of Lucentis (ranibizumab injection) 0.5 mg for the treatment of patients with diabetic retinopathy independent of the presence of diabetic macular edema (DME). Data from the Phase 3, prospective, multicenter, randomized clinical trial Protocol S are included in this section.

The safety profile of Lucentis (ranibizumab injection) 0.3 mg for the treatment of diabetic retinopathy in patients with diabetic macular edema was previously demonstrated and was approved February 6, 2015.

7.1.2 Categorization of Adverse Events

The protocol adequately defined an adverse event. Each investigator evaluated study participants for adverse events, volunteered and elicited, at each study visit. An Adverse Event Form was completed to document a description of the event, onset, severity, treatment required, outcome and relatedness to the use of the study medication.

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

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety of Lucentis (ranibizumab injection) 0.5 mg dosed monthly has been demonstrated in the original BLA which was originally approved June 30, 2006 and subsequent supplemental applications. The safety of Lucentis (ranibizumab injection) 0.3 mg dosed monthly for the treatment of diabetic macular edema and diabetic retinopathy in patients with diabetic macular edema was previously demonstrated and approved February 2015.

The 2 year data from Protocol S (ML27976) submitted in this supplemental BLA are included in this section. Pooled data across indications was not submitted and is not reviewed in this review.

7.2 Adequacy of Safety Assessments

The overall clinical experience was adequate. The conduct of the Phase 3 Study Protocol S was adequate and well-controlled. An adequate number of patients with diabetic retinopathy with and without diabetic macular edema were exposed to ranibizumab to assess potential safety and efficacy issues during the development program. The study design was appropriate.

Safety and tolerability of the 0.5 mg ranibizumab regimen was compared with panretinal photocoagulation (PRP) through the 2 year (Week 104) time period. All safety analyses were performed in all patients as treated.

There were two analysis populations for safety: safety-evaluable eyes and safety-evaluable subjects.

- The population for safety-evaluable eyes included randomized eyes that received at least one study treatment (ranibizumab or PRP). Treatment groups for this population were defined according to the actual treatment received during the 2-year period up to and including the 2-year visit:
 - If an eye received only one study treatment (ranibizumab or PRP), the treatment group for this eye was that of the active treatment received.
 - If an eye received both study treatments (ranibizumab and PRP), the treatment group for this eye was as randomized.
- The population for safety-evaluable subjects included randomized subjects that received at least one study treatment (ranibizumab or PRP). Treatment groups for this population were defined separately for subjects with one and two study eyes enrolled, according to the actual treatment received during the 2-year period up to and including the 2-year visit.

The treatment group for subjects who received treatment in one study eye was defined as follows:

- If a subject received only one active treatment (ranibizumab or PRP), the treatment group for this subject was that of the active treatment received.
 - If a subject received both study treatments (ranibizumab and PRP), the treatment group for this subject was as randomized.
- The treatment group for subjects who received treatment in two study eyes was defined as follows:
 - If a subject received only one active treatment (ranibizumab or PRP), the treatment group for this subject was that of the active treatment received.
 - If a subject received both study treatments (ranibizumab and PRP), the treatment group for this subject was bilateral treatment (subjects with two study eyes enrolled).

- The following group definitions for the safety-evaluable subjects are used in this report:
 - Subjects with 1 study eye randomized to the ranibizumab group are referred to as: subjects in the ranibizumab-1 study eye group
 - Subjects with 1 study eye randomized to the PRP group are referred to as: subjects in the PRP-1 study eye group
 - Subjects with 2 study eyes randomized are referred to as: subjects in the 2-study eyes group.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At Year 1 of the study, eyes in the ranibizumab group received a mean number of injections of 7.1 per eye; the mean number of injections in eyes with and without baseline DME was 8.5 and 6.7, respectively. Between 1 and 2 years of the study, a mean number of ranibizumab injections of 3.3 per eye were received in the ranibizumab group; the mean number of injections in eyes with and without baseline DME was 3.9 and 3.1, respectively.

At Year 2 of the study, the mean number of ranibizumab injections received was 3.4 per eye in the PRP group. Eyes in the PRP subgroup with baseline DME received a mean number of ranibizumab injections of 8.2 per eye. Eyes in the PRP subgroup without baseline DME received a mean number of ranibizumab injections of 2.0 per eye.

**Table 7.2.1-1
Randomized Treatment vs. Actual Treatment Received Through 2 Years:
Randomized Eyes**

Actual Treatment Received	Ranibizumab 0.5 mg N=191	PRP Total N=203
Ranibizumab only	178 (93.2%)	0
PRP only	0	93 (45.8%)
Ranibizumab and PRP	13 (6.8%)	110 (54.2%)

Source: Module 5.3.5.1 CSR Protocol S Table 51

Actual treatment received includes study treatment received from Randomization to the 2-year visit in the study eye only.

Table 7.2.1-2
Extent of Ranibizumab Exposure Through 2 Years by Baseline DME Status:
Safety-Evaluable Eyes

	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
n	191	42	149	203	46	157
Total	1983	522	1461	687	377	310
Mean (SD)	10.4 (4.9)	12.4 (5.1)	9.8 (4.7)	3.4 (4.9)	8.2 (5.9)	2.0 (3.5)
0	0	0	0	93 (45.8%)	0	93 (59.2%)
1	0	0	0	22 (10.8%)	6 (13.0%)	16 (10.2%)
2	2 (1.0%)	0	2 (1.3%)	11 (5.4%)	4 (8.7%)	7 (4.5%)
3	5 (2.6%)	0	5 (3.4%)	11 (5.4%)	3 (6.5%)	8 (5.1%)
4	11 (5.8%)	0	11 (7.4%)	6 (3.0%)	3 (6.5%)	3 (1.9%)
5	16 (8.4%)	3 (7.1%)	13 (8.7%)	10 (4.9%)	2 (4.3%)	8 (5.1%)
6	22 (11.5%)	6 (14.3%)	16 (10.7%)	8 (3.9%)	3 (6.5%)	5 (3.2%)
7	11 (5.8%)	1 (2.4%)	10 (6.7%)	8 (3.9%)	4 (8.7%)	4 (2.5%)
8	8 (4.2%)	2 (4.8%)	6 (4.0%)	5 (2.5%)	2 (4.3%)	3 (1.9%)
9	16 (8.4%)	2 (4.8%)	14 (9.4%)	5 (2.5%)	3 (6.5%)	2 (1.3%)
10	16 (8.4%)	2 (4.8%)	14 (9.4%)	4 (2.0%)	2 (4.3%)	2 (1.3%)
11	12 (6.3%)	4 (9.5%)	8 (5.4%)	1 (0.5%)	0	1 (0.6%)
12	13 (6.8%)	1 (2.4%)	12 (8.1%)	4 (2.0%)	2 (4.3%)	2 (1.3%)
13	8 (4.2%)	1 (2.4%)	7 (4.7%)	2 (1.0%)	2 (4.3%)	0
14	10 (5.2%)	5 (11.9%)	5 (3.4%)	1 (0.5%)	0	1 (0.6%)
15	5 (2.6%)	2 (4.8%)	3 (2.0%)	2 (1.0%)	2 (4.3%)	0

	Ranibizumab 0.5 mg				PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)	
Prior to 2 Years (Maximum = 26)							
16	8 (4.2%)	3 (7.1%)	5 (3.4%)	2 (1.0%)	2 (4.3%)	0	
17	8 (4.2%)	2 (4.8%)	6 (4.0%)	3 (1.5%)	2 (4.3%)	1 (0.6%)	
18	4 (2.1%)	1 (2.4%)	3 (2.0%)	2 (1.0%)	1 (2.2%)	1 (0.6%)	
19	6 (3.1%)	2 (4.8%)	4 (2.7%)	1 (0.5%)	1 (2.2%)	0	
20	5 (2.6%)	3 (7.1%)	2 (1.3%)	2 (1.0%)	2 (4.3%)	0	
21	4 (2.1%)	1 (2.4%)	3 (2.0%)	0	0	0	
22	1 (0.5%)	1 (2.4%)	0	0	0	0	
≥ 23	0	0	0	0	0	0	

Source: Module 2.7.3 SCE Protocol S Table 1

Table 7.2.1-3
Extent of PRP Exposure Through 2 Years by Baseline DME Status:
Safety-Evaluable Eyes

	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Number of eyes receiving PRP	13 (6.8%)	6 (14.3%)	7 (4.7%)	203 (100.0%)	46 (100.0%)	157 (100.0%)
Number of eyes receiving supplemental PRP (after initial PRP), n	1 (0.5%)	1 (2.4%)	0	92 (45.3%)	15 (32.6%)	77 (49.0%)
Number of days from randomization to first PRP						
Median	429.0	450.5	429.0	222.0	364.0	219.0
Min – Max	29 – 721	29 – 721	312 – 673	35 – 707	43 – 638	35 – 707
Number of PRP sittings performed						
1	---	---	---	109 (53.7%)	28 (60.9%)	81 (51.6%)
2	---	---	---	80 (39.4%)	17 (37.0%)	63 (40.1%)
3	---	---	---	14 (6.9%)	1 (2.2%)	13 (8.3%)

Source: SCE Protocol S Table 2

Reviewer’s Comment:

Thirteen eyes (6.8%) in the ranibizumab treatment group required PRP during the 2 year study.

7.2.2 Explorations for Dose Response

There was no exploration of dose response performed in the study submitted.

7.2.3 Special Animal and/or In Vitro Testing

No pharmacology toxicology information was submitted in the supplemental BLA.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of ranibizumab.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events associated with the anti-VEGF class of drugs are known. The safety analysis included evaluation and reporting of these potential adverse reactions: elevated IOP, intraocular inflammation, AEs at the injection site (i.e., subconjunctival hemorrhage, scleral pathology, etc.), non-infectious inflammatory eye reactions due to immunogenicity, arterial thromboembolic events, and systemic reactions.

7.3 Major Safety Results

The overall incidence of adverse events was consistent with those reported in patients receiving ranibizumab treatment for other approved indications. There were no new ocular or non-ocular safety findings identified in the submitted study.

7.3.1 Deaths

**Table 7.3.1-1
Deaths and Cause of Death Through 2 Years
Safety-Evaluable Subjects**

Subject ID	Age / Sex	Study Day of Death	No. of RBZ injection prior to AE Onset	Baseline DME Status	SAE which Resulted in Death
One Study Eye - Ranibizumab					
(b) (6)	54/F	120	4	No	Congestive cardiac failure
(b) (6)	40/M	516	14	Yes	Chronic renal failure Left ventricular failure
(b) (6)	54/M	310	5	Yes	Cardiac failure Coronary artery disease Myelodysplastic syndrome
(b) (6)	66/M	610	14	No	Death, unknown cause
(b) (6)	44/M	373	8	No	Cardiac arrest Chronic kidney disease Hypoxic-ischemic encephalopathy
(b) (6)	53/F	491	6	Yes	History of angina Death, unknown cause
One Study Eye - PRP					
(b) (6)	43/M	538	5	Yes	Chronic renal failure, dialysis
(b) (6)	27/F	525	---	No	Complications of DM, gastroparesis
(b) (6)	74/F	167	1	Yes	Brain neoplasm
(b) (6)	54/M	126	---	No	Cardiac arrest
Two Study Eyes					
(b) (6)	62/M	514	15	Yes	Cerebrovascular accident
(b) (6)	53/M	120	5	No	Myocardial infarction
(b) (6)	58/M	469	11	No	Chronic renal failure, congestive heart failure
(b) (6)	48/F	408	11	No	Death, unknown cause

Reviewer's Comment:

Fourteen deaths occurred during the 2-year conduct of Protocol S. The primary causes of death were common in the diabetic patient population.

7.3.2 Nonfatal Serious Adverse Events

Table 7.3.2 – 1
Ocular Serious Adverse Events in the Study Eye Through 2 Years
Safety Evaluable Eyes

MedDRA System Organ Class Preferred Term	Ranibizumab 0.5 mg			PRP		
	Overall N=191	Eyes with Baseline DME N=42	Eyes without Baseline DME N=149	Overall N=203	Eyes with Baseline DME N=46	Eyes without Baseline DME N=157
Total number of eyes with at least one adverse event	3 (1.6%)	1 (2.4%)	2 (1.3%)	2 (1.0%)	2 (4.3%)	0
Eye Disorders						
Vitreous hemorrhage	1 (0.5%)	1 (2.4%)	0	2 (1.0%)	2 (4.3%)	0
Sudden visual loss	1 (0.5%)	0	1 (0.7%)	0	0	0
Visual impairment	1 (0.5%)	0	1 (0.7%)	0	0	0
Vitreous floaters	1 (0.5%)	0	1 (0.7%)	0	0	0
Infections and infestations						
Endophthalmitis	1 (0.5%)	0	1 (0.7%)	0	0	0

Source: Module 2.7.3 CSR SCE, Table 9

Reviewer’s Comment: *Three subject eyes in the ranibizumab group experienced at least one ocular serious adverse event during the 2-year study period.*

Table 7.3.2 – 2
Non-Ocular Serious Adverse Events Occurring in > 1 Subject in Any Treatment Group
Through 2 Years by Baseline DME Status
Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye						Subjects with 2 Study Eyes	
	Ranibizumab		PRP					
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89	Subjects with Baseline DME N=29	Subjects without Baseline DME N=60		
Total number of subjects with at least 1 adverse event	13 (61.9%)	36 (44.4%)	9 (36.0%)	33 (37.1%)	10 (34.5%)	28 (46.7%)		
Infections and infestations								
Pneumonia	1 (4.8%)	2 (2.5%)	0	2 (2.2%)	1 (3.4%)	3 (5.0%)		
Localized infection	0	3 (3.7%)	0	1 (1.1%)	1 (3.4%)	1 (1.7%)		
Sepsis	1 (4.8%)	1 (1.2%)	0	0	2 (6.9%)	1 (1.7%)		
Cellulitis	0	2 (2.5%)	1 (4.0%)	1 (1.1%)	0	0		
Osteomyelitis	0	2 (2.5%)	0	0	1 (3.4%)	1 (1.7%)		
Urinary tract infection	0	1 (1.2%)	0	0	0	4 (6.7%)		
General disorders and administration site conditions								
Chest pain	3 (14.3%)	5 (6.2%)	1 (4.0%)	2 (2.2%)	0	2 (3.3%)		
Death	2 (9.5%)	1 (1.2%)	0	2 (2.2%)	0	2 (3.3%)		
Asthenia	2 (9.5%)	2 (2.5%)	0	1 (1.1%)	0	0		
Impaired healing	0	1 (1.2%)	0	2 (2.2%)	0	1 (1.7%)		
Peripheral edema/swelling	0	3 (3.7%)	1 (4.0%)	0	0	1 (1.7%)		
Surgical and medical procedures								
Stent placement	0	0	0	2 (2.2%)	0	2 (3.3%)		
Toe amputation	1 (4.8%)	1 (1.2%)	0	0	1 (3.4%)	0		

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye				Subjects with 2 Study Eyes	
	Ranibizumab		PRP		Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89		
Coronary arterial stent insertion	0	0	0	0	0	2 (3.3%)
Surgery	0	0	0	0	1 (3.4%)	1 (1.7%)
Metabolism and nutrition disorders						
Dehydration	0	1 (1.2%)	1 (4.0%)	0	1 (3.4%)	1 (1.7%)
Diabetic ketoacidosis	0	3 (3.7%)	1 (4.0%)	0	0	0
Fluid overload	2 (9.5%)	1 (1.2%)	0	0	0	0
Hyperglycemia	0	0	0	0	0	3 (5.0%)
Ketoacidosis	0	1 (1.2%)	0	0	1 (3.4%)	0
Cardiac disorders						
Cardiac failure congestive	2 (9.5%)	4 (4.9%)	1 (4.0%)	1 (1.1%)	0	2 (3.3%)
Myocardial infarction ^a	1 (4.8%)	1 (1.2%)	0	3 (3.4%)	0	3 (5.0%)
Coronary artery disease	1 (4.8%)	2 (2.5%)	0	0	0	0
Cardiac arrest	1 (4.8%)	1 (1.2%)	0	0	0	0
Coronary artery stenosis	1 (4.8%)	0	0	0	0	1 (1.7%)
Renal and urinary disorders						
Acute kidney injury	0	5 (6.2%)	1 (4.0%)	0	1 (3.4%)	2 (3.3%)
Renal failure	3 (14.3%)	2 (2.5%)	1 (4.0%)	1 (1.1%)	0	2 (3.3%)
Chronic kidney disease	1 (4.8%)	1 (1.2%)	1 (4.0%)	1 (1.1%)	0	0
Nephropathy	2 (9.5%)	0	0	0	0	1 (1.7%)
Renal impairment	0	2 (2.5%)	0	1 (1.1%)	0	0
Nephrolithiasis	0	0	0	0	0	2 (3.3%)
Nervous system disorders						

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MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye						Subjects with 2 Study Eyes	
	Ranibizumab			PRP			Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects with Baseline DME N=89	Subjects without Baseline DME N=89			
Cerebrovascular accident	0	3 (3.7%)	2 (8.0%)	2 (2.2%)	1 (3.4%)	0		
Syncope	1 (4.8%)	2 (2.5%)	0	0	0	0		
Hypoxic-ischemic encephalopathy	1 (4.8%)	1 (1.2%)	0	0	0	0		
Respiratory, thoracic and mediastinal disorders								
Dyspnea	4 (19.0%)	1 (1.2%)	1 (4.0%)	4 (4.5%)	0	2 (3.3%)		
Cough	1 (4.8%)	1 (1.2%)	0	3 (3.4%)	0	0		
Oropharyngeal pain	0	1 (1.2%)	0	2 (2.2%)	0	0		
Injury, poisoning and procedural complications								
Foot fracture	2 (9.5%)	1 (1.2%)	1 (4.0%)	0	0	0		
Fall	0	0	1 (4.0%)	1 (1.1%)	1 (3.4%)	0		
Vascular disorders								
Hypertension	2 (9.5%)	2 (2.5%)	0	1 (1.1%)	1 (3.4%)	2 (3.3%)		
Arterial occlusive disease	0	0	0	0	0	2 (3.3%)		
Hypotension	0	0	0	0	0	2 (3.3%)		
Gastrointestinal disorders								
Vomiting	0	4 (4.9%)	2 (8.0%)	0	1 (3.4%)	1 (1.7%)		
Nausea	0	4 (4.9%)	2 (8.0%)	0	0	0		
Abdominal pain	0	4 (4.9%)	0	0	0	0		
Impaired gastric emptying	0	0	2 (8.0%)	1 (1.1%)	0	0		
Investigations								
Blood glucose increased	0	2 (2.5%)	0	0	1 (3.4%)	0		

MedDRA System Organ Class Preferred Term	Subjects with 1 Study Eye				Subjects with 2 Study Eyes	
	Ranibizumab		PRP		Subjects with Baseline DME N=29	Subjects without Baseline DME N=60
	Subjects with Baseline DME N=21	Subjects without Baseline DME N=81	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89		
Musculoskeletal and connective tissue disorders	0	1 (1.2%)	0	3 (3.4%)	0	0
Pain in extremity	0	1 (1.2%)	0	3 (3.4%)	0	0
Skin and subcutaneous tissue disorders	0	2 (2.5%)	0	0	1 (3.4%)	0
Diabetic foot	0	2 (2.5%)	0	0	1 (3.4%)	0
Skin ulcer	0	0	0	0	2 (6.9%)	0
Ear and labyrinth disorders	0	0	0	0	0	0
Vertigo	0	0	0	3 (3.4%)	0	0

Source: Module 2.7.3 SCS Table 6

a Includes adverse events: myocardial infarction and acute myocardial infarction **b** Included adverse event preferred terms of cerebrovascular accident and ischemic stroke.

Reviewer’s Comment: *Serious non-ocular adverse events occurred in 44% of subjects in the ranibizumab-1 study eye subgroup without baseline DME. The most common non-ocular serious adverse events were chest pain, acute kidney injury, congestive heart failure, and pneumonia.*

7.3.3 Dropouts and/or Discontinuations

No ocular adverse events led to permanent treatment discontinuation.

Table 7.3.3 – 1
Non-Ocular Adverse Events Through 2 Years that Led to Permanent Treatment Discontinuation
Safety Evaluable Eyes

Preferred Term	Subjects with 1 Study Eye		Subjects with 2 Study Eyes N=89
	Ranibizumab N=102	PRP N=114	
Total number of subjects with at least 1 adverse event	6 (5.9%)	2 (1.8%)	4 (4.5%)
Death	2 (2.0%)	2 (1.8%)	2 (2.2%)
Cardiac arrest	1 (1.0%)	0	0
Cardiac failure	1 (1.0%)	0	0
Cardiac failure congestive	1 (1.0%)	0	0
Coronary artery disease	1 (1.0%)	0	0
Myocardial infarction	0	0	1 (1.1%)
Cerebrovascular accident	1 (1.0%)	0	1 (1.1%)
Hypoxic-ischemic encephalopathy	1 (1.0%)	0	0
White blood cell disorder	1 (1.10%)	0	0
Type 2 diabetes mellitus	1 (1.0%)	0	0
Chronic kidney disease	1 (1.10%)	0	0
Extubation	1 (1.0%)	0	2 (2.2%)

Source: Module 5.3.5.1 CSR Table 60

Note: Counts represent number of subjects reporting the event; individual event counts may not add up to system totals because of multiple events per subject.

Reviewer’s Comment: *Six subjects in the ranibizumab-1 study eye and 4 subjects in the ranibizumab -2 study eye treatment groups had non-ocular adverse events which led to treatment discontinuation. Death was the most common non-ocular adverse event to lead to treatment discontinuation.*

7.3.4 Significant Adverse Events

Antiplatelet Trialists' Collaboration events (vascular deaths, unknown cause deaths, non-fatal myocardial infarctions, non-fatal cerebrovascular accidents) were reported in 4 (19.0%) subjects in the ranibizumab- study eye subgroup with baseline DME and 6 (7.4%) subjects without baseline DME. In the 2 study eyes group, APTC events were reported in 1 (3.4%) subject with baseline DME and 5 (8.3%) subjects without baseline DME. In the PRP-1 study eye group, APTC events were reported in 2 (8.0%) subjects with baseline DME and 7 (7.9%) subjects without baseline DME.

Table 7.3.4-1 Deaths, Myocardial Infarctions, and Cerebrovascular Accidents Through 2 Years by Baseline DME Status Safety Evaluable Subjects

Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Any Event	6 (12.0%)	13 (9.2%)	4 (16.0%)	8 (9.0%)
Deaths				
Overall	4 (8.0%)	6 (4.3%)	2 (8.0%)	2 (2.2%)
Vascular	1 (2.0%)	2 (1.4%)	0	1 (1.1%)
Non-vascular	1 (2.0%)	2 (1.4%)	2 (8.0%)	1 (1.1%)
Unknown cause	2 (4.0%)	2 (1.4%)	0	0
MI or CVA				
Overall	3 (6.0%)	8 (5.7%)	2 (8.0%)	6 (6.7%)
MI				
Overall	2 (4.0%)	4 (2.8%)	0	4 (4.5%)
Fatal	0	1 (0.7%)	0	0
Non-fatal	2 (4.0%)	3 (2.1%)	0	4 (4.5%)
CVA				
Overall	1 (2.0%)	4 (2.8%)	2 (8.0%)	2 (2.2%)
Fatal	1 (2.0%)	0	0	0
Non-fatal	0	4 (2.8%)	2 (8.0%)	2 (2.2%)
APTC events (vascular deaths, unknown cause deaths, non-fatal MIs, non-fatal CVAs)	5 (10.0%)	11 (7.8%)	2 (8.0%)	7 (7.9%)

Note: Subjects with 2 study eyes enrolled are included in the Ranibizumab group. Subjects with 2 study eyes enrolled are considered to have baseline DME if at least 1 study eye has baseline DME.

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Reviewer's Comment: *The proportion of patients who experienced APTC events was the same for the ranibizumab (8%) and PRP (8%) treatment groups.*

7.3.5 Submission Specific Primary Safety Concerns

There are no submission specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

**Table 7.4.1-1
Ocular Adverse Events in the Study Eye Occurring in ≥ 10% of Eyes in Any Treatment Group Through 2 Years
Safety Evaluable Eyes**

MedDRA System Organ Class Preferred Term	Ramibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Total number of eyes with at least 1 adverse event	152 (79.6%)	36 (85.7%)	116 (77.9%)	164 (80.8%)	39 (84.4%)	125 (79.6%)
Vitreous floaters	54 (28.3%)	8 (19.0%)	46 (30.9%)	56 (27.6%)	13 (28.3%)	43 (27.4%)
Vitreous hemorrhage	39 (20.4%)	10 (23.8%)	29 (19.5%)	54 (26.6%)	10 (21.7%)	44 (28.0%)
Vision blurred	32 (16.8%)	9 (21.4%)	23 (15.4%)	54 (26.6%)	15 (32.6%)	39 (24.8%)
Visual acuity reduced	26 (13.6%)	8 (19.0%)	18 (12.1%)	38 (18.7%)	12 (26.1%)	26 (16.6%)
Eye pain	27 (14.1%)	7 (16.7%)	20 (13.4%)	30 (14.8%)	4 (8.7%)	26 (16.6%)
Dry eye	16 (8.4%)	4 (9.5%)	12 (8.1%)	15 (7.4%)	6 (13.0%)	9 (5.7%)
Visual impairment	14 (7.3%)	4 (9.5%)	10 (6.7%)	15 (7.4%)	2 (4.3%)	13 (8.3%)
Conjunctival hemorrhage	21 (11.0%)	5 (11.9%)	16 (10.7%)	7 (3.4%)	4 (8.7%)	3 (1.9%)
Cataract	10 (5.2%)	4 (9.5%)	6 (4.0%)	16 (7.9%)	4 (8.7%)	12 (7.6%)
Retinal detachment	9 (4.7%)	1 (2.4%)	8 (5.4%)	17 (8.4%)	4 (8.7%)	13 (8.3%)
Eye pruritus	12 (6.3%)	3 (7.1%)	9 (6.0%)	12 (5.9%)	3 (6.5%)	9 (5.7%)
Lacrimation increased	11 (5.8%)	4 (9.5%)	7 (4.7%)	12 (5.9%)	3 (6.5%)	9 (5.7%)
Retinal hemorrhage	13 (6.8%)	3 (7.1%)	10 (6.7%)	10 (4.9%)	2 (4.3%)	8 (5.1%)
Photopsia	8 (4.2%)	0	8 (5.4%)	13 (6.4%)	5 (10.9%)	8 (5.1%)

MedDRA System Organ Class Preferred Term	Ranibizumab 0.5 mg			PRP		
	Overall N=191 n (%)	Eyes with Baseline DME N=42 n (%)	Eyes without Baseline DME N=149 n (%)	Overall N=203 n (%)	Eyes with Baseline DME N=46 n (%)	Eyes without Baseline DME N=157 n (%)
Eye irritation	13 (6.8%)	2 (4.8%)	11 (7.4%)	7 (3.4%)	3 (6.5%)	4 (2.5%)
Eye disorder	7 (3.7%)	1 (2.4%)	6 (4.0%)	10 (4.9%)	3 (6.5%)	7 (4.5%)
Macular fibrosis	6 (3.1%)	2 (4.8%)	4 (2.7%)	11 (5.4%)	6 (13.0%)	5 (3.2%)
Unevaluable event	21 (11.0%)	6 (14.3%)	15 (10.1%)	24 (11.8%)	9 (19.6%)	15 (9.6%)

Source: Module 2.7.3 SCS Table 6

Reviewer’s Comment:

The frequency of ocular adverse events was similar between the ranibizumab with and without baseline DME treatment groups, and between ranibizumab and PRP treatment groups.

The most common ocular adverse events in the ranibizumab without baseline DME treatment group was vitreous floaters, vitreous hemorrhage, blurred vision, eye pain, visual acuity reduced and conjunctival hemorrhage. All of these adverse events except vitreous hemorrhage are included in the Lucentis package insert.

Table 7.4.1-2
Non-Ocular Adverse Events Occurring in $\geq 10\%$ of Eyes in Any Treatment Group
Through 2 Years by Baseline DME
Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Ranibizumab		PRP	
	Subjects with Baseline DME N=50	Subjects without Baseline DME N=141	Subjects with Baseline DME N=25	Subjects without Baseline DME N=89
Total number of subjects with at least 1 adverse event	45 (90.0%)	128 (90.8%)	20 (80.0%)	71 (79.8%)
Infections and infestations				
Nasopharyngitis	10 (20.0%)	18 (12.8%)	3 (12.0%)	7 (7.9%)
Influenza	7 (14.0%)	13 (9.2%)	2 (8.0%)	6 (6.7%)
General disorders and administration site conditions				
Unevaluable event	3 (6.0%)	5 (3.5%)	3 (12.0%)	1 (1.1%)
Nervous system disorders				
Headache	6 (12.0%)	20 (14.2%)	3 (12.0%)	11 (12.4%)
Respiratory, thoracic and mediastinal disorders				
Cough	5 (10.0%)	19 (13.5%)	1 (4.0%)	6 (6.7%)
Dyspnea	5 (10.0%)	10 (7.1%)	1 (4.0%)	6 (6.7%)
Gastrointestinal disorders				
Nausea	5 (10.0%)	15 (10.6%)	4 (16.0%)	6 (6.7%)
Vomiting	3 (6.0%)	14 (9.9%)	3 (12.0%)	3 (3.4%)
Injury, poisoning and procedural complications				
Fall	7 (14.0%)	8 (5.7%)	3 (12.0%)	4 (4.5%)
Vascular disorders				
Hypertension	12 (24.0%)	25 (17.7%)	6 (24.0%)	14 (15.7%)
Metabolism and nutrition disorders				
Diabetes mellitus inadequate control	2 (9.5%)	10 (12.3%)	4 (16.0%)	6 (6.7%)
Renal and urinary disorders				
Nephropathy	7 (14.0%)	11 (7.8%)	2 (8.0%)	7 (7.9%)
Renal disorder	2 (4.0%)	6 (4.3%)	3 (12.0%)	2 (2.2%)
Chronic kidney disease	1 (2.0%)	4 (2.8%)	3 (12.0%)	1 (1.1%)
Cardiac disorders				
Coronary artery disease	6 (12.0%)	6 (4.3%)	0	2 (2.2%)
Psychiatric disorders				
Depression	0	2 (1.4%)	3 (12.0%)	4 (4.5%)

Source: Module 2.7.3 SCS Table 7; March 24, 2017 submission in response to Information Request #4

Reviewer's Comment: *Ninety percent of ranibizumab subjects and eighty percent of PRP subjects experienced at least one adverse event. The rates of non-ocular adverse events were similar in ranibizumab and PRP subjects.*

The most common non-ocular adverse events in ranibizumab subjects which occurred more frequently in the ranibizumab group were hypertension, nasopharyngitis, headache, influenza, nephropathy, nausea and fall.

7.4.2 Laboratory Findings

Laboratory data were not collected during this study.

7.4.3 Vital Signs

Vital signs were not assessed during this study.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in this study.

7.4.5 Special Safety Studies/Clinical Trials

Special safety studies/clinical trials were not conducted.

7.4.6 Immunogenicity

Immunogenicity was not evaluated in this study.

7.5 Other Safety Explorations

Safety analysis was based on an evaluation of other safety parameters, as well, which included visual acuity (best corrected), intraocular pressure, ocular signs by slit lamp examination and indirect ophthalmoscopy the results of which are included throughout the safety review. For details refer to the Common Adverse Event table in Section 7.4.1.

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events was not demonstrated in this study.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not demonstrated in this study.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not identified.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not identified.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not identified.

7.6 Additional Safety Evaluations

There were no additional safety evaluations.

7.6.1 Human Carcinogenicity

There is no known carcinogenic potential.

7.6.2 Human Reproduction and Pregnancy Data

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

7.6.3 Pediatrics and Assessment of Effects on Growth

Diabetic retinopathy does not occur in the pediatric age group. Therefore, a pediatric waiver was sought and granted for this indication.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no potential for overdose, abuse or withdrawal.

7.7 Additional Submissions / Safety Issues

The 120-Day Safety Update was submitted on January 9, 2017.

For reference, BL 1215156/S-114 is based on the efficacy and safety data from a Jaeb Center for Health Research-sponsored study entitled “Prompt Panretinal Photocoagulation Versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy” (Protocol S) with a data cut off in January 2015. The first patient was enrolled in February 2012, and the study is currently ongoing with patients having been treated up to approximately 4 years.

For this safety update, Genentech reviewed the safety data of subjects without baseline diabetic macular edema (DME) in the ranibizumab arm in the ongoing Protocol S study with a data cut off of December 6, 2016. The types of ocular and non-ocular adverse events observed were consistent with the safety profile observed for this subgroup at the primary endpoint at 2 years and the well-established safety profile of Lucentis.

No additional safety information for Lucentis in patients with diabetic retinopathy (DR) without DME has become available from other clinical studies. Lucentis is currently not approved for DR patients without DME in the U.S. or outside the U.S. and no post-marketing safety data are available for this safety update.

Genentech concludes that the safety profile for the DR without baseline DME population remains favorable, and that the benefit-risk profile in this population remains unchanged. As such, no modifications to the recommended labeling submitted with BL 125156/S-114 are proposed at this time.

8 Postmarket Experience

Lucentis (ranibizumab injection) has been marketed since its approval on June 30, 2006. Routine postmarketing reporting and the results of clinical trials have been reviewed as submitted. All relevant post market experience data has been incorporated into the product labeling.

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

No Advisory Committee Meeting was scheduled regarding this application.

9.3 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number: BLA 125156 / S-114

Submission Date(s): October 18, 2016

Applicant: Genentech, Inc.

Product: Lucentis (ranibizumab injection) 0.5%

Reviewer: Rhea A. Lloyd, MD

Date of Review: November 10, 2016

Covered Clinical Studies (Name and/or Number):
Protocol S

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: Protocol S: 180 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>Seven</u> .		
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: <u>None</u>		
Significant payments of other sorts: <u>Seven</u>		
Proprietary interest in the product tested held by investigator: <u>None</u>		
Significant equity interest held by investigator in sponsor of covered study: <u>None</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>None</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Disclosure: Financial Interests and Arrangements of Clinical Investigators

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*.⁴ 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.

The clinical study, Protocol S, was conducted by the Jaeb Center for Health Research (JCHR). The JCHR also held the study database and was responsible for all data management activities. Genentech was not involved in the conduct of the study, but did provide ranibizumab and funds to the JCHR to defray costs.

Of the 180 investigators that participated in Protocol S, 7 (4%) reported disclosable financial interests in Genentech. These disclosures are summarized in the table below. The number of subjects affected is 29 (9%), therefore, the potential for bias is low.

⁴ See [web address].

The risk of potential bias is further mitigated by the fact that the maximum number of subjects randomized at any given site was no more than 7% of the total number of subjects enrolled.

The design of Protocol S minimized the potential for bias by any investigator. By the study design, there was no single investigator or sub-investigator who had influence that could affect the results of the trial. The study was multicenter, double-blinded, randomized with an active control. The actual treatment given to individual subjects is determined by a randomization schedule.

In summary, the risk of bias for Protocol S was limited and JHCR and Genentech assessed that the financial disclosures' findings described above do not affect the integrity or reliability of the results from this study.

Table 1
Summary of Financial Disclosure Information Collected for Investigators in Protocol S

Clinical Site Number	Name	Subject Enrollment	Disclosure
		(b) (6)	Consultancy and lectures in total: indeterminate value ^a Board membership and lectures in total: \$69,997 Consultancy, lectures and development of educational presentations in total: \$59,997 Consultancy, lectures and travel in total: \$89,997 Consultancy and lectures in total: \$59,999 Board membership, consultancy, lectures, and travel/accommodations/meeting expenses in total: \$59,997 Board Membership, consultancy, lectures and manuscript preparation in total: \$119,997
(b) (6)			

9.4 Labeling Recommendations

Following is the approved labeling with the applicant's proposed changes to the carton labeling as submitted on December 6, 2016, and the package insert as submitted in this Supplement on January 13, 2017.

The applicant's additions are noted by underline and deletions by.
The reviewer's additions are noted by underline and deletions by.

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

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

/s/

RHEA A LLOYD
03/29/2017

WILLIAM M BOYD
03/29/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

PHARMACOLOGY REVIEW(S)

**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: sBLA 125156/S-114
Supporting document/s: 838
Applicant's letter date: 10-18-2016
CDER stamp date: 10-18-2016
Product: Lucentis (Ranibizumab injection)
Indication: Treatment of all diabetic retinopathy patients,
independent of diabetic macular edema status
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: Lois Almoza

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125156/S-114 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-114 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-114.

The purpose of this supplemental BLA is to support a revision of the LUCENTIS® USPI to include all diabetic retinopathy patients, independent of diabetic macular edema status. The proposed USPI revisions are based on the efficacy and safety data from a Jaeb Center for Health Research-sponsored study entitled “Prompt Panretinal Photocoagulation Versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy” (Protocol S). The Jaeb Center for Health Research did not transfer any sponsor obligations, thus they were responsible for all aspects of study conduct.

The intended dose for LUCENTIS® in the treatment of diabetic retinopathy is 0.3 mg (0.05 mL) administered by intravitreal injection once a month. This dosing regimen is the same previously approved by the FDA for diabetic retinopathy in patients with diabetic macular edema. No new nonclinical studies were submitted with this supplemental BLA. As such, there are no new concerns from the nonclinical perspective.

The recommended revisions to the nonclinical sections presented below are the same as those recommended for BLA 125156/S-111.

Labeling Recommendations:

Sponsor’s proposed text	Reviewer’s recommendations
<p>8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy</p>	<p>8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy</p>
<p>(b) (4)</p>	<p><u>Risk Summary</u></p> <p>There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.</p> <p>Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose [see <i>Animal Data</i>].</p> <p>Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab</p>

(b) (4)

[see *Clinical Pharmacology (12.1)*], treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data

Animal Data

An embryofetal 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.

8.2 Lactation

Risk Summary

There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion. 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.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child

from ranibizumab.

8.3 Females and Males of Reproductive Potential

Infertility

No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action of ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of fertility

Animal studies have not been conducted to determine the carcinogenic potential of ranibizumab. Based on the anti-VEGF mechanism of action of ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity [*see Females and Males of Reproductive Potential (8.3)*].

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/s/

MARIA I RIVERA
12/27/2016

LORI E KOTCH
12/27/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

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

CLINICAL STUDIES

BLA/Serial #: 125156/S-114

Drug Name: Lucentis® (ranibizumab injection)

Indication(s): Treatment of Patients with Diabetic Retinopathy

Applicant: Genentech, Inc.

Date(s): Stamp Date: October 18, 2016
PDUFA Date: April 18, 2017
Review Date: March 24, 2017

Review Priority: Priority

Biometrics Division: IV

Statistical Reviewer: Solomon Chefo, Ph.D.

Concurring Reviewers: Yan Wang, Ph.D., Team Leader

Medical Division: Division of Transplant and Ophthalmology Products (DTOP)

Clinical Team: Rhea Lloyd, MD, Medical Officer
William Boyd, MD, Team Leader

Project Manager: Lois Almoza

Keywords: Cochran–Mantel–Haenszel, Diabetic Retinopathy Severity Score

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1 EXECUTIVE SUMMARY

Diabetic Retinopathy (DR), a vascular disease of the retina, is a leading cause of vision loss among adults with diabetes. Diabetic Macular Edema (DME), a consequence of DR, is the most common cause of vision loss among patients with DR. LUCENTIS® (ranibizumab injection) 0.3 mg administered monthly was first approved for the treatment of DME based on the results of two Phase 3 studies (referred to as RIDE and RISE), and was later approved for the treatment of DR in patients with DME based on additional DR-related analyses in the same studies. In this sBLA, the applicant is seeking to broaden the indication of treatment of DR regardless of DME status.

This sBLA was based on the data from the Diabetic Retinopathy Clinical Research Network sponsored Phase 3 study (referred to as ‘Protocol S’) with a cross reference to the RISE and RIDE studies. The protocol was not submitted for review by DTOP as the study results were initially not intended for a regulatory submission. Although the primary study objective was to determine the non-inferiority of ranibizumab 0.5 mg (ranibizumab group) to prompt panretinal photocoagulation (PRP¹ group) in visual acuity in eyes with proliferative diabetic retinopathy (PDR), the primary efficacy focus in this sBLA was based on the proportions of eyes with ≥ 2 -step and ≥ 3 -step improvement in the DR severity score (DRSS) at Year 2. Of note, these endpoints were used to support the approval of monthly ranibizumab 0.3 mg injection for the treatment of DR in patients with DME.

Protocol S was a 5-year multicenter, randomized, active-controlled study. This sBLA included all efficacy and safety data collected during the first 2 years as the study is on-going. The study enrolled a total of 305 DR subjects (394 eyes) with or without DME; 75 subjects (88 eyes) had DME in at least one eye. Randomization was stratified by baseline DME status. Subjects with a single eligible eye (N=216) were randomized in a 1:1 ratio to ranibizumab or PRP group. Subjects with two eligible eyes (n=89) received PRP in one eye and ranibizumab in the other eye randomly. Eyes in the ranibizumab group received ranibizumab 0.5 mg monthly injection for the first four injections and as needed (PRN) afterwards. Eyes in the PRP group received PRP at baseline. Eyes in both treatment groups received ranibizumab injection as needed if eyes had DME at baseline or developed DME during the study; and also received PRP treatment during the study if protocol-specified criteria were met.

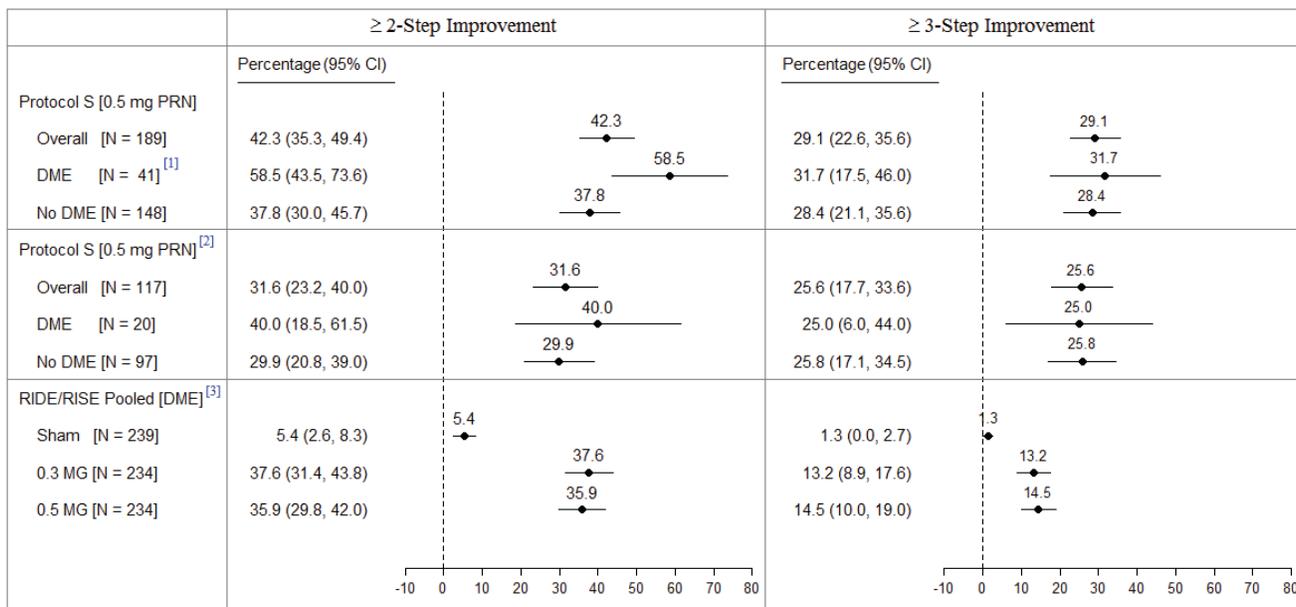
The ranibizumab treatment yielded significant improvements in DR severity from baseline at Year 2 regardless of the DME status. In the ranibizumab group, as shown in [Figure 1](#), the proportion of eyes with ≥ 2 -step improvement was 42% (95% CI: 35% to 49%) for all eyes, 59% (95% CI: 43% to 74%) for eyes with DME, and 38% (95% CI: 30% to 46%) for eyes without DME. The proportion of eyes with ≥ 3 -step improvement was 29% (95% CI: 23% to 36%) for all eyes, 32% (95% CI: 18% to 46%) for eyes with DME, and 28% (95% CI: 21% to 36%) for eyes without DME. The numerically better improvement shown in eyes with DME than those without DME might be influenced by the number of ranibizumab injections received and the imbalance in the DR severity at baseline. Specifically, eyes with DME received more ranibizumab injections (see [Table 22](#)) and more eyes with DME had worse DR severity at baseline (see [Table 5](#)). It is worth noting that ranibizumab treatment showed significantly larger improvement in eyes with worse DR severity at baseline; for example, 60% of all eyes with high risk PDR or

¹ According to the study protocol, PRP was the current standard treatment for PDR; PRP is not an FDA-approved therapy for PDR.

worse at baseline (DRSS > 65) achieved ≥ 2 -step improvement whereas only 32% of all eyes with moderate PDR or better at baseline (DRSS ≤ 65) achieved ≥ 2 -step improvement (Figure 2).

Overall, the DRSS improvements with the ranibizumab treatment were substantial in light of the progressively worsening nature of the disease and in comparison to the very low placebo (sham) rates (5% for ≥ 2 -step improvement and 1% for ≥ 3 -step improvement) in the RIDE/RISE studies.

Figure 1: DRSS Improvement in Protocol S and in the Pooled RISE/RISE Studies at Year 2: Ranibizumab Group



^[1] Protocol S had much better results than RISE/RISE studies because it enrolled a greater number of eyes with DRSS > 65.

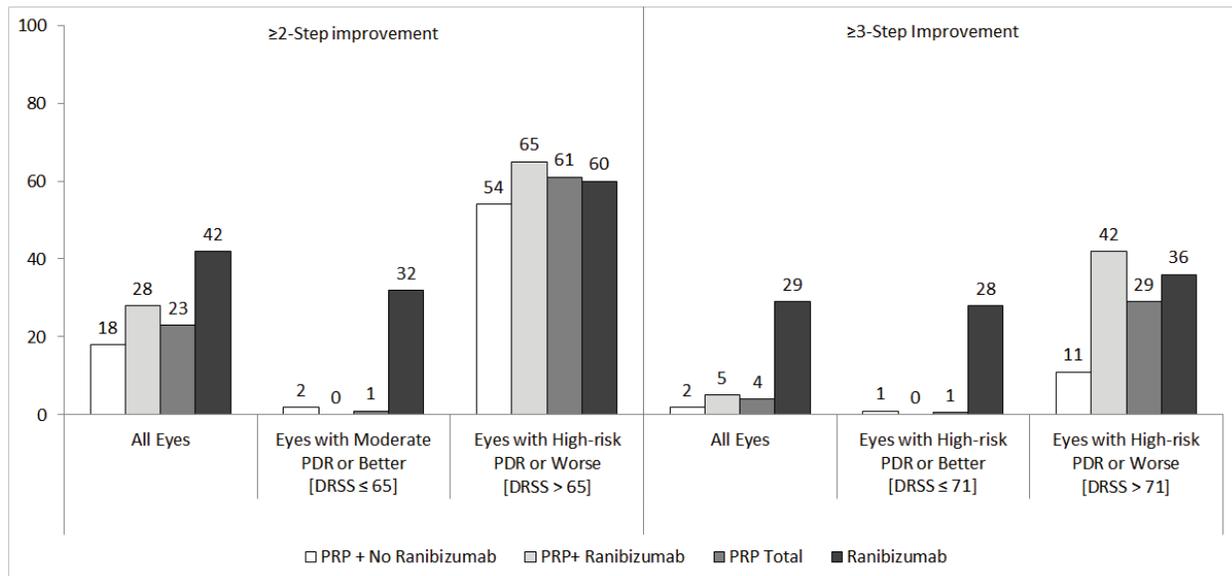
^[2] This analysis was conducted on eyes with DRSS ≤ 65 in an attempt to resemble the RISE/RISE studies in baseline DRSS.

^[3] Source: Table 7 of statistical review for the RISE/RISE studies; and Table 1 of Applicant Pre-sBLA post-meeting package.

For the PRP group, the rates of improvement in DRSS at Year 2 were much lower than those in the ranibizumab group: 23% for ≥ 2 -step improvement and 3.5% for ≥ 3 -step improvement (See Figure 2). These lower rates, however, are partially due to the nature of the DRSS grading scheme involved with the PRP-induced scars (see Section 3.2.4.1). For example, almost all eyes with high risk PDR or better at baseline (DRSS ≤ 71), which accounted for 89.5% of the eyes in the PRP group, could not meet the criteria of ≥ 3 -step improvement due to the nature of the DRSS grading scheme. Consequently, the endpoint of ≥ 3 -step improvement could not be meaningfully interpreted for eyes with baseline DRSS ≤ 71 .

In those subgroups of eyes where the DR endpoints could be meaningfully interpreted for both treatment groups (See Figure 2), the study demonstrated significant treatment benefit in both groups. While both groups had similar rates of ≥ 2 -step improvement (approximately 60%), the ranibizumab group had a numerically higher rate of ≥ 3 -step improvement than the PRP group (36% vs. 29%). The treatment benefit with ranibizumab was also seen in eyes in the PRP group that received ranibizumab injection during the study. For example, the eyes that were treated with both PRP and ranibizumab injection had a much higher rate of ≥ 3 -step improvement than those treated with PRP only (42% vs. 11%). Note that 54% of eyes in the PRP group received at least one ranibizumab injection with an average of 6.3 injections prior to Year 2.

Figure 2: Percentage of Eyes with ≥ 2 -Step and ≥ 3 -Step improvement in DRSS at Year 2 (mITT Population, LOCF)



mITT: modified intent-to-treat (mITT) population which included all randomized eyes with a valid DRSS score at baseline

In summary, ranibizumab 0.5 mg PRN in Protocol S demonstrated substantial improvement in DR severity in eyes with DR regardless of DME status.

Based on the treatment benefit of ranibizumab 0.5 mg PRN in DR patients with and without DME, the applicant requested to broaden the indication of treatment of DR regardless of DME for the approved dose of ranibizumab 0.3 mg monthly. The applicant established a bridge between the ranibizumab 0.5 mg PRN dosing regimen used in Protocol S to the approved ranibizumab 0.3 mg monthly dosing regimen based on the following considerations: (i) the consistency of results for ≥ 2 -step² improvement at Year 2 across doses and regimens in Protocol S and in the RISE/RIDE studies (see Figure 1), (ii) comparable averaged amounts of ranibizumab between the 0.3 mg monthly and 0.5 mg PRN regimens over the first year for eyes without DME, (iii) similar results for monthly 0.3 mg and 0.5 mg in the RISE/RIDE studies (see Figure 1), and (iv) similarity in disease pathology in DR patients with or without DME. The applicant's justification for a bridge between monthly 0.3 mg and 0.5 mg PRN appeared acceptable from the reviewer perspective.

The reviewer concludes that this application provides evidence of efficacy of ranibizumab 0.3 mg monthly dosing for a broad indication of treatment of DR regardless of DME status. The conclusion is based on the totality of evidence from the RIDE/RISE studies and the additional information in DR patients with and without DME provided in the Protocol S study, and the well-established safety profile of monthly ranibizumab 0.3 mg dosing and knowledge that the same dosing regimen is already approved for the treatment of DR in patients with DME.

² Protocol S had much better results for ≥ 3 -step improvement at Year 2 than RISE/RIDE studies because it enrolled a greater number of eyes with high-risk PDR or worse at baseline (See Table 5).

2 INTRODUCTION

2.1 Overview

Lucentis® (ranibizumab injection, 0.3 mg) was approved for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema in February 2015. In this sBLA, the applicant seeks to extend the use of ranibizumab 0.3 mg for a broad indication of treatment of DR regardless of DME status.

2.1.1 Class and Indication

Diabetic retinopathy (DR) is a vascular disease of the retina which affects patients with diabetes; diabetes damages the blood vessels in the retina overtime, and DR occurs when these blood vessels leak blood and other fluids in the retina. DR is a leading cause of blindness in adult.

DR is classified into two types:

- i) *Nonproliferative diabetic retinopathy (NPDR)*: the early stage of the disease where blood vessels in the retina are weakened and begin to leak fluid into the retina. This stage of the disease may be asymptomatic.
- ii) *Proliferative diabetic retinopathy (PDR)*: the more advanced form of the disease. It mainly occurs when many of the blood vessels in the retina close, preventing enough blood flow. To supply blood where the original vessels closed, the retina grows new blood vessels (neovascularization); however, the new blood vessels are abnormal and do not supply the retina with proper blood flow. PDR may cause more severe vision loss than NPDR.

Two intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies were recently approved for the treatment of DR in patients with DME: Lucentis® (ranibizumab injection) 0.3 mg administered monthly and Eylea® (aflibercept injection) 2.0 mg administered once a month for the first five injections and then once every two months. Currently there is no FDA-approved therapy for the broad indication of DR treatment.

According to the applicant, PRP is the current standard of treatment for PDR. Of note, PRP is not an FDA-approved therapy for PDR.

2.1.2 History of Drug Development

Lucentis (ranibizumab injection) was approved in the U.S. for multiple indications since 2006. Ranibizumab 0.3 mg monthly injection was first approved for the treatment of DME based on the results of two Phase 3 studies (RIDE and RISE) in patients with DME, and was later approved for the treatment of DR in patients with DME based on the results of additional DR analyses in the RISE and RIDE studies. Efficacy evaluation for the indication of treatment of DME was based on improvement in visual acuity at year 2 and for the indication of treatment of DR in patients with DME was based on ≥ 3 -step and ≥ 2 -step improvement in the diabetic retinopathy severity score (DRSS) at year 2.

In this sBLA, the applicant seeks to expand the currently approved ranibizumab 0.3 mg monthly dose to all DR patients regardless of DME status. Support for this indication was based on the data from the Diabetic Retinopathy Clinical Research Network (DRCR.net) sponsored study

(referred to as ‘Protocol S’) with a cross reference from the RISE and RIDE studies submitted in support of the approved indication.

Protocol S was not submitted for review by DTOP prior to study initiation as it was initially intended for a different objective.

Meeting Correspondence

On September 1, 2015, a Type B Pre-sBLA meeting was held (under IND 08633) to discuss the potential use of Protocol S to support ranibizumab 0.3 mg monthly injection for a broad indication of treatment of DR regardless of DME status. During the meeting; DTOP expressed concerns regarding the design, control, primary endpoint, and the interpretability of the Protocol S data. Specifically pointing out that: (i) the endpoints used to support the sBLA are defined post-hoc, and asked the applicant to provide explanation that the treatment effect seen in the submission are not due to chance alone; (ii) potential bias due to the inability to adequately mask the treatment groups, and to address the impact of this potential bias on the data; (iii) how a bridge could be established from ranibizumab 0.5 mg PRN dosing regimen used in Protocol S to the current approved ranibizumab 0.3 mg monthly dosing and how Protocol S data complements the data from the RISE/RIDE studies to support a broad DR indication; and (iv) to describe the chronology of events known to the applicant regarding Protocol S to understand the integrity of the analyses and post-hoc nature of the proposal.

On September 15, 2015, the applicant submitted additional information to address the Division’s concerns; the complete responses are presented in Section 3.0 of the post-meeting package located at <\\cdsesub1\evsprod\IND008633\0830>.

Reviewer’s Note:

Based on review of the applicant responses and review of the data, the reviewer determined that: (i) the treatment effect seen in the Protocol S does not appear by chance alone despite the DR-related endpoints to support the sBLA were defined post-hoc (see detail in the review) and (ii) even though patients and investigators in Protocol S were unmasked to the treatment assignment, image evaluators for DRSS outcomes were masked to treatment assignment and to images from previous visits. Furthermore, since patients in one treatment arm could receive the treatment randomized to the other arm based on protocol-defined criteria during the course of the study, the chance of unmasking the image readers is very minimal. Therefore, the reviewer believes that the impact of potential bias on the data due to the inability to adequately mask the treatment groups is minimal.

Finally, the applicant established a bridge between the ranibizumab 0.5 mg PRN dosing regimen used in Protocol S to the approved ranibizumab 0.3 mg monthly dosing regimen based on the following considerations: (i) the consistency of results for ≥ 2 -step improvement at Year 2 across doses and regimens in Protocol S and in the RISE/RIDE studies, (ii) comparable averaged amounts of ranibizumab between 0.3 mg monthly and 0.5 mg PRN over the first year for eyes without DME, (iii) similar results for monthly 0.3 mg and monthly 0.5 mg in the RISE/RIDE studies, and (iii) similarity in disease pathology in DR patients with or without DME. The applicant’s justification for a bridge based on the consistency of results and comparable averaged dose between monthly 0.3 mg and 0.5 mg PRN appeared acceptable from the reviewer perspective (See detail in [Section 3.2.4.6](#)). Regarding the disease pathology, we defer to the medical reviewer.

2.1.3 Specific Studies Reviewed

The sBLA submission was based on data from Protocol S study with a cross reference from the RISE and RIDE studies. Protocol S study enrolled a total of 305 subjects (394 eyes) from 57 clinical sites in the United States.

A brief summary of Protocol S study is presented in [Table 1](#) below.

Table 1: Study Summary

Design/ Study Objective	Treatment /Sample Size	Treatment Period	Study Population
Phase III, prospective, multicenter, randomized, and active-controlled study. Protocol S Primary Objective: To determine if visual acuity outcomes at 2 years in eyes with PDR that received ranibizumab with deferred PRP were non-inferior to those in eyes that received standard prompt PRP therapy.	Ranibizumab 0.5 mg PRN (monthly for the first 4 injections and as needed afterwards) / (n = 191 eyes) Prompt PRP/ (n = 203 eyes) - Study enrolled a total of 394 eyes from 305 subjects	Two years treatment period with three years follow-up.	Subjects \geq 18 years of age with: - Type 1 or Type 2 diabetes, at least 1 study eye with PDR. - BCVA score of at least 24 ETDRS letters. - No prior PRP (prior PRP is defined as \geq 100 burns placed previously outside of the posterior pole)

PDR: proliferative Diabetic Retinopathy; PRP: Panretinal photocoagulation; PRN: pro re nata (as needed); ETDRS-DRSS = Early Treatment Diabetic Retinopathy Study-Diabetic Retinopathy Severity Scale.

2.2 Data Sources

The data source for this review included: the original study protocol (including one amendment) and the analysis plan prepared by DRCR.net; and the applicant’s clinical study report, the statistical analysis plan, the analysis and tabulation datasets, and SAS codes to perform the analyses. These were provided in electronic submission and are located at <\\CDSESUB1\evsprod\BLA125156\0187>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There was no major issue identified with respect to the quality and integrity of the submitted datasets. Although the datasets were not fully CDISC compliant, the submission included certain elements of the CDISC standards. In addition, the *Reviewer's Guide Document* and the *Define.pdf* files included in the submission provided sufficient detail to access and easily work with the datasets. As such, minimal effort was needed to process the data.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

(i) Study Design

Protocol S was a Phase III, multicenter, randomized, active-controlled study primarily designed to determine if ranibizumab 0.5 mg PRN with deferred PRP (ranibizumab group) was non-inferior to prompt PRP (PRP group) in visual acuity at 2 years in eyes with PDR.

The study enrolled a total of 305 subjects (394 eyes) ≥ 18 years of age with Type 1 or Type 2 diabetes that had a BCVA score of ≥ 24 letters (approximate Snellen equivalent 20/320), and had at least one eye with DR (with or without DME). A single eye was eligible for a total of 216 subjects and both eyes were eligible for the remaining 89 subjects at the time of randomization.

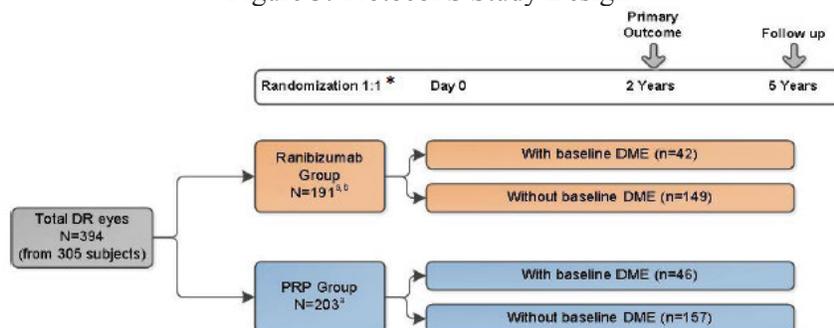
Subjects with a single eligible eye were randomized in a 1:1 ratio to either ranibizumab or PRP group. Subjects with both eligible eyes randomly received PRP in one eye and ranibizumab in the second eye based on the eye's central subfield thickness (CST) at baseline; that is, subjects with both eligible eyes were randomized in a 1:1 ratio to either Group A (eye with greater CST assigned to PRP and second eye assigned to ranibizumab) or Group B (eye with greater CST assigned to ranibizumab and second eye assigned to PRP); if both eyes had the same CST, the right eye was considered with the greater CST. Randomization was stratified by site and presence of DME at baseline; for the purpose of stratification, presence of DME was defined in the study as $CST \geq 250$ microns on Zeiss Stratus OCT (or equivalent thickness on spectral domain OCT machine).

Eyes assigned in the ranibizumab group received ranibizumab 0.5 mg monthly through week 12, and as needed afterwards based on appearance of neovascularization; eyes in this group received PRP during the study if protocol defined retreatment criteria were met. Eyes assigned to the PRP group received PRP at baseline (based on pre-specified PRP protocol) if no DME at baseline, or received PRP within 14 days of ranibizumab injection if DME was present at baseline for which ranibizumab was needed (Note: if performed on the same day, PRP was given prior to injection); eyes in this group received supplemental PRP if neovascularization had worsened after the initial PRP. In both treatment groups, eyes with DME at baseline or eyes that developed DME during the study received ranibizumab injection for DME as needed.

Protocol S was a single-mask study: subjects, investigators, and study coordinators were not masked to treatment assignments; but reading center graders who evaluated the fundus photographs (for DRSS assessment) and the visual acuity and optical coherence tomography

(OCT) technicians were all masked to treatment assignments. Furthermore, reading center graders for the fundus photographs were also masked to images from previous visits in addition to the treatment assignment. Figure 3 below shows the flow chart for Protocol S study design.

Figure 3: Protocol S Study Design



* Randomization was stratified by presence or absence of center-involved DME at baseline. Presence of DME was defined on OCT central subfield as ≥ 250 microns on Zeiss Stratus OCT (or equivalent thickness on spectral domain OCT machine)

Source: Figure 4 of Applicant Clinical Overview

The total study duration is 5 years with a 3-year treatment period and a 2-year follow-up period. The sBLA included efficacy and safety data up to 2 years (completed in 2015), and patients are currently being followed.

Efficacy assessments were made based on best corrected visual acuity (BCVA), OCT to measure central retinal thickness (CRT), and fundus photographs (FP) to measure DRSS. BCVA was tested from a distance of 3 meters. Eyes in both treatment groups had BCVA assessments at baseline, weeks 16, 32, 52, 68, 84, and 104 for the first 2 years of the study; but eyes in the ranibizumab group were assessed more frequently. OCT, FA and DRSS assessments were made at baseline, week 52 (year 1), and week 104 (year 2).

The DRSS, a validated method measuring DR severity, was graded according to a 12-step severity score and characterized DR severity into levels ranging from absent to advanced PDR (that is, macular center detached) (See Table 2).

Table 2: Steps for EDTRS-Diabetic Retinopathy Severity Score

Combined DR severity levels (as text)	Combined DR severity levels	Severity Level ^[2]
DR Absent	10, 12	1
DR questionable, microaneurysms only	14A-14C, 14Z, 15, 20	2
Mild NPDR	35A-35F	3
Moderate NPDR	43A, 43B	4
Moderately Sever NPDR	47A-47D	5
Severe NPDR	53A-53E	6
Prior PRP ^[1]; without active PDR	60	7
Mild PDR	61A, 61B	7
Moderate PDR	65A-65C	8
High-risk PDR	71A - 71D	9
High-risk PDR	75	10
Advanced PDR, macula center attached	81	11
Advanced PDR, macula center attached	85A, 85B	12
Missing or cannot grade	90	90

^[1] Defined as ≥ 100 burns outside of the posterior pole; ^[2] used to determine step change in DRSS

Reviewer’s Note:

The applicant indicated that DRSS = 60 was assigned to fundus images with definite PRP scars where PDR was inactive and DRSS < 60 were not assessed if PRP scars were detected; as such, images with definite PRP scars were given DRSS ≥ 60. Due to this grading scheme, a majority of PRP-treated eyes could not achieve ≥ 2-step improvement (See more detail later).

(ii) Study Endpoints Included in Protocol S

The mean change in BCVA from baseline at year 2 was the primary efficacy endpoint in Protocol S Study. This endpoint was used to determine the non-inferiority of ranibizumab 0.5 mg PRN to PRP in visual acuity.

The protocol also included the following DR-related secondary endpoints:

- 1) Proportion of eyes in the ranibizumab group with ≥ 2-step improvement from baseline in DRSS at 2 years
- 2) Proportion of eyes with ≥ 2-step worsening from baseline in DRSS at 2 years and
- 3) Proportion of eyes in the ranibizumab group with DR severity of NPDR or better at 2 years

Reviewer’s Note:

It is worth noting that the protocol defined the endpoint of “≥ 2-step improvement from baseline in DRSS at 2 years” only for the ranibizumab group, not for the PRP group. Although no rationale was provided in the protocol, this may be due to the consideration that a majority of PRP-treated eyes could not achieve this endpoint due to the nature of the DRSS grading scheme (see Section 3.2.4.1 for detailed discussions). On the other hand, the protocol defined the endpoint “≥ 2-step worsening from baseline in DRSS at 2 years” for both treatment groups as this endpoint is meaningful for the targeted PDR patient populations. Of note, this endpoint is not meaningful for patients with NPDR or better (see Section 3.2.4.4 for detailed discussions).

(iii) DR-related Endpoints Defined to Support the sBLA

For the purpose of this sBLA, the applicant’s SAP included the following DR-related endpoints to support ranibizumab for the expanded indication:

- 1) The proportion of eyes with ≥3-step and ≥2-step improvement in DRSS from baseline at year 1 and year 2.
- 2) The proportion of eyes with ≥3-step and ≥2-step worsening in DRSS from baseline at year 1 and year 2.
- 3) Proportion of eyes with ≥ 2-step improvement from baseline in DRSS from PDR at baseline to NPDR at 1 year or 2 years

It should be noted that the DR-related endpoints in items (i) and (ii) were used in the RISE and RIDE studies which resulted in the approval of monthly ranibizumab 0.3 mg injection for the treatment of DR in patients with DME.

3.2.2 Statistical Methodology

i) Analysis Populations

Three analysis populations were defined in the applicant's SAP: the intent-to-treat (ITT) population which included all randomized eyes and the safety-evaluable eyes (for ocular safety summary) and safety-evaluable subjects (for non-ocular safety summary) which included all randomized subjects that received at least one study treatment. All efficacy analyses were based on randomized eyes with a valid DRSS score at baseline: here after referred to as modified-ITT (mITT) population.

ii) Efficacy Analyses

For the analyses of the DR-related endpoints, the applicant performed both stratified and un-stratified analyses based on the mITT population with missing data imputed using the last observation carried forward (LOCF) method; the stratified analyses adjusted for baseline DME status and number of eyes enrolled.

In the un-stratified analyses, a point and two-sided 95% CI estimates for the proportions in each treatment group and for the difference in the proportion between the treatment groups was based on normal approximation for binomial proportions. In the stratified analyses, a weighted point and two-sided 95% CI estimates for the proportions in each treatment group and for the difference in the proportion between the treatment groups was performed using the Cochran–Mantel–Haenszel (CMH) weights and normal approximation to the binomial distribution of the weighted estimates. The results based on the stratified and un-stratified analyses were very similar except for minor numerical differences.

The applicant also performed sensitivity analyses using multiple imputation (MI) method and observed case analysis (without missing data imputation) to assess the robustness of the efficacy results.

The reviewer also performed additional sensitivity analyses by first treating all eyes with missing DRSS data as non-responders and then using MI based on placebo (sham) rate. In the reviewer's MI approach, the observed sham rate for the proportion of subjects with ≥ 2 -step and ≥ 3 -step improvement in the RISE/RIDE studies were used to generate 20 imputed datasets. The results from the 20 datasets were then combined using SAS PROC MIANALYZE. The sensitivity analyses results were consistent with the LOCF method used in the primary analysis. See [Section 3.2.4.4](#) for more detail.

Even though change in visual acuity is not the main focus in this sBLA, the mean change in BCVA at each time points was also summarized in this review and comparison between the treatment groups was made using analysis of covariance (ANCOVA) model with treatment and baseline BCVA as covariates. To account for the correlation within subjects with two study eyes, a mixed-model repeated measure (MMRM) was performed.

Reviewer's Note:

In the SAP, the applicant planned to perform treatment comparisons for the DR-related endpoints; however, the applicant did not present and discuss the results of such comparisons in the clinical summary of efficacy as well as in the clinical section of the proposed label. In

the proposed label only the results from the ranibizumab group were presented. The applicant did not explain why the sBLA focused only on the results from the ranibizumab group.

Despite the lack of explanation in the application, a valid treatment comparison based on all eyes could not be made in the sBLA since a majority of eyes in the PRP group (due to the nature of the DRSS grading scheme) could not achieve the DR-related endpoints (see Section 3.2.4.1 for detailed discussions). A valid treatment comparison, however, could be made in the subgroups of eyes with high-risk PDR or worse at baseline because these eyes in both treatment groups could have the potential to achieve these endpoints. Treatment comparisons in these subgroups were made using the analyses methods above without taking the correlation from eyes from the same subject into account (note: the correlation for the change in DRSS between two eyes from the same subject was weak: $r = 0.21$ at year 1 and $r = 0.13$ at year 2).

To assess the impact of ignoring the correlation, the reviewer conducted treatment comparison based on bootstrap re-sampling approach that takes the correlation into account. The bootstrap analysis was based on 500 samples generated from the original data with replacement. The resampling was done separately for subjects with a single eye enrolled and with both eyes enrolled to maintain the correlation from eyes from the same subject in each sample. For each bootstrap sample, the difference in proportion was calculated and the 2.5 and 97.5 percentiles were used to determine the 95% confidence interval for the treatment difference. Except for minor numerical differences, the bootstrap approach yielded consistent result (See Table 10 and Table 11).

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

3.2.3.1 Subject Disposition

The summary of subject disposition and the primary reasons for study discontinuation from treatment prior to 2 years are shown in Table 3. The disposition summary was presented by subjects even though eyes were the unit of analysis in the study.

Table 3: Subject Disposition
(ITT Population)

	Subjects with only one eye enrolled		Subjects with both eyes enrolled	Total (N=305)
	PRP (N=114)	Ranibizumab (N=102)	PRP/Ranibizumab ^[1] (N = 89)	
Eyes completing study through 1 year	109 (95.6)	98 (96.1)	83 (93.3)	290 (95.1)
Eyes completing study through 2 years	101 (88.6)	88 (86.3)	75 (84.3)	264 (86.6)
Eyes discontinued from treatment prior to 2 years ^[1]	13 (11.4)	14 (13.7)	14 (15.7)	41 (13.4)
Death	4 (3.5)	6 (5.9)	4 (4.5)	14 (4.6)
Lost to follow up	6 (5.3)	5 (4.9)	5 (5.6)	16 (5.2)
Site withdraws subject	1 (0.9)	0 (0.0)	2 (2.2)	3 (1.0)
Subject formally withdrew consent in writing	0 (0.0)	1 (1.0)	0	1 (0.3)
Subject requests to withdraw (not in writing)	2 (1.8)	2 (2.0)	3 (3.4)	7 (2.3)

Based on reviewer analysis

^[1] Five subjects discontinued treatment prior to year 2, but completed the study

A total of 305 subjects (394 eyes) were enrolled in the study: 114 and 102 subjects with a single eligible eye in the PRP and ranibizumab group, respectively, and 89 subjects with both eyes eligible (one eye in the PRP group and the other eye in the ranibizumab group). A total of 75 subjects (88 eyes) had DME at baseline: 46 subjects with a single eye enrolled (25 in PRP and 21 in ranibizumab,) and 29 subjects with both eyes enrolled (13 of the 29 subjects had DME in both eyes at baseline). The majority of subjects completed the 2-years treatment period. A total of 41 subjects (~13%) discontinued treatment prior to 2 years: 27 subjects (~12%) with a single eye enrolled (13 in PRP and 14 in ranibizumab) and 14 subjects (~16%) with both eyes enrolled discontinued. From the total of 41 subjects that discontinued prior to 2 years, 11 subjects with a single eye enrolled had DME at baseline (5 in PRP and 6 in ranibizumab) and 4 subjects with two eyes enrolled had DME in at least one eye.

The main reasons for discontinuation prior to 2 years were due to death (~5%) and lost-to-follow up (~5%); no subjects discontinued due to AE. A total of 14 subjects died prior to 2 years: 10 subjects with single eye enrolled (4 in PRP and 6 in ranibizumab) and 4 subjects with both eyes enrolled. From the total of 14 subjects that died prior to 2 years, 5 subjects with single eye enrolled (2 in PRP and 3 in ranibizumab) and 1 subject with both eyes enrolled had DME.

Overall the discontinuation rates prior to 2-years were comparable between the treatment groups; however, the rate of discontinuation in both groups was slightly higher in subjects with DME at baseline than those without DME.

3.2.3.2 Demographic and Baseline Characteristics

The summaries of the demographic and baseline disease characteristics for eyes in the ITT population are shown in Table 4. The majority of subjects were white (~71%), more than half were male (~56%), and about a quarter were Hispanic or Latino. The average age of subjects was about 51 years with <10% of subjects were ≥65 years (range 20 to 83). The demographic characteristics were well balanced across the treatment groups.

In terms of baseline disease characteristics: eyes enrolled in the study had a median duration of diabetes of about 17 years (range: 0 – 49 years); the median duration was slightly longer in eyes without DME than with DME by 3 years. The mean HbA1C at baseline was about 9%, and about 62% and 56% of eyes in the PRP and ranibizumab group, respectively, had HbA1C > 8% at baseline. In both treatment groups, more eyes without DME at baseline had HbA1C > 8% compared to eyes with DME.

Table 4: Summary of Demographic and Baseline Disease Characteristics (ITT Population)

	PRP			Ranibizumab		
	Overall (N=203)	DME (N=46)	No DME (N=157)	Overall (N=191)	DME (N=42)	No DME (N=149)
Age (in years)						
Mean (SD)	50.5 (11.7)	53.2 (11.4)	49.7 (11.7)	50.4 (11.5)	52.7 (9.2)	49.8 (12.0)
Median	51.0	55.5	49.0	51.0	54.0	50.0
Min-Max	22 - 83	23 - 83	22 - 83	20 - 79	27 - 68	20 - 79
Age category						
<65	187 (92.1)	42 (91.3)	145 (92.4)	173 (90.6)	40 (95.2)	133 (89.3)
≥65	16 (7.9)	4 (8.7)	12 (7.6)	18 (9.4)	2 (4.8)	16 (10.7)

	PRP			Ranibizumab			
	Overall (N=203)	DME (N=46)	No DME (N=157)	Overall (N=191)	DME (N=42)	No DME (N=149)	
Sex							
Male	111 (54.7)	23 (50.0)	88 (56.1)	108 (56.5)	27 (64.3)	81 (54.4)	
Female	92 (45.3)	23 (50.0)	69 (43.9)	83 (43.5)	15 (35.7)	68 (45.6)	
Race							
Black or African American	43 (21.2)	6 (13.0)	37 (23.6)	40 (20.9)	8 (19.0)	32 (21.5)	
White	143 (70.4)	38 (82.6)	105 (66.9)	135 (70.7)	32 (76.2)	103 (69.1)	
Other	17	2	15	16	2	14	
Ethnicity							
Hispanic or Latino	51 (25.1)	9 (19.6)	42 (26.8)	48 (25.1)	13 (31.0)	35 (23.5)	
Not Hispanic or Latino	144 (70.9)	35 (76.1)	109 (69.4)	136 (71.2)	24 (57.1)	112 (75.2)	
Unknown/not reported	8 (3.9)	2 (4.3)	6 (3.8)	7 (3.7)	5 (11.9)	2 (1.3)	
Number of Eyes Enrolled							
One Study Eye	114 (56.2)	25 (54.3)	89 (56.7)	102 (53.4)	21 (50.0)	81 (54.4)	
Two study Eye	89 (43.8)	21 (45.7)	68 (43.3)	89 (46.6)	21 (50.0)	68 (45.6)	
Duration of Diabetes (years) ^[2]							
Mean (SD)	16.6 (9.8)	15.3 (12.1)	17.0 (9.0)	18.0 (10.8)	15.7 (9.9)	18.7 (11.0)	
Median	16.0	13.5	17.0	18.0	15.0	18.0	
Min-Max	0 - 49	0 - 49	0 - 46	0 - 60	0 - 46	0 - 60	
HbA1c							
Mean (SD)	9.10 (2.16)	8.65 (2.27)	9.23 (2.12)	9.02 (2.27)	9.03 (2.66)	9.02 (2.15)	
Median	8.85	7.80	9.05	8.60	8.00	8.60	
Min-Max	4.8 - 17.3	5.7 - 17.3	4.8 - 15.6	4.8 - 17.3	5.7 - 17.3	4.8 - 16.2	
HbA1c Group							
≤ 8%	73 (36.0)	25 (54.4)	48 (30.6)	78 (40.8)	22 (52.4)	56 (37.6)	
> 8%	125 (61.6)	21 (45.7)	104 (66.2)	106 (55.5)	19 (45.2)	87 (58.4)	
Missing	5 (2.5)	0	5 (3.2)	7 (3.7)	1 (2.4)	6 (4.0)	
Visual acuity (VA, in letters)							
Mean (SD)	75.2 (12.5)	64.7 (13.0)	78.3 (10.5)	75.0 (12.8)	63.8 (14.1)	78.1 (10.5)	
Median	78.0	69.5	81.0	77.0	68.5	80.0	
Min-Max	26 - 96	26 - 78	41 - 96	25 - 97	25 - 78	32 - 97	
CI-DME by BCVA							
Absent	Overall	141 (69.5)	0	141 (89.8)	136 (71.2)	0	136 (91.3)
	BCVA ≤ 78	64 (31.5)	0	64 (40.8)	62 (32.5)	0	62 (41.6)
	BCVA > 78	77 (37.9)	0	77 (49.0)	74 (38.7)	0	74 (49.7)
Present	Overall	62 (30.5)	46 (100)	16 (10.2)	55 (28.8)	42 (100)	13 (8.7)
	BCVA ≤ 78	46 (22.7)	46 (100)	0	42 (22.0)	42 (100)	0
	BCVA > 78	16 (7.9)	0	16 (10.2)	13 (6.8)	0	13 (8.7)
CST (microns)							
Mean (SD)	308.0 (108.5)	458.1 (126.8)	265.1 (48.1)	295.5 (85.9)	393.2 (123.6)	266.5 (37.6)	
Median	276.0	436.5	261.0	277.0	336.5	268.0	
Min-Max	165 - 779	256 - 779	165 - 584	153 - 857	250 - 857	153 - 370	
CST group							
< 250	51 (25.1)	0	51 (32.5)	52 (27.2)	0	52 (34.9)	
≥ 250	150 (73.9)	46 (100)	104 (66.2)	137 (71.7)	42 (100)	95 (63.8)	
Missing	2 (1.0)	0	2 (1.3)	2 (1.0)	0	2 (1.3)	

Source: Table 2 and Table 3 of applicant clinical study report. CI-DME: center-involved diabetic macular edema; CST: central subfield thickness

^[1]: Baseline DME was defined as presence of center-involved DME with baseline BCVA ≤ 75 letters;

^[2]: According to the protocol, duration of diabetes was assigned zero years if a subject was not precise and records were not available.

The study enrolled eyes with baseline BCVA > 24 letters (approximate Snellen equivalent of 20/230); and the mean baseline BCVA between the treatment groups was comparable. In both groups, eyes with DME at baseline had a lower mean BCVA (64 letters) compared to eyes without DME (78 letters). Similarly, the overall mean CST at baseline was comparable between the treatment groups and the majority of eyes had CST ≥ 250 microns; in both groups, eyes with DME at baseline had a higher mean CST at baseline than eyes without DME.

Approximately 30% of eyes (117/394) in the study had center-involved DME (CI-DME) at baseline, and 88 of the 117 eyes with CI-DME had baseline BCVA ≤ 78 letters. In Protocol S study, eyes with CI-DME and BCVA ≤ 78 at baseline were considered as having DME at baseline (see column 3 and 6 of Table 4). This DME definition was intended to match the RISE and RIDE studies that enrolled DME patients with BCVA score 24 to 78 letters.

Summary of DR Severity Score at Baseline:

The summary of the baseline DRSS data in the Protocol S study is shown in Table 5 below; the DRSS data for the pooled RISE and RIDE studies are also presented for comparison purpose. The distribution of the DRSS data at baseline was comparable between the treatment groups in Protocol S study; about 11% of eyes in the study had severe NPDR or better (DRSS ≤ 53), 49% had mild-to-moderate PDR (DRSS = 60, 61, 65), and 37% had high-risk PDR or worse (DRSS > 65). More eyes with DME (~46%) had high-risk PDR or worse at baseline than eyes without DME (~35%) while fewer eyes with DME (~43%) had mild-to-moderate PDR at baseline than eyes without DME (~52%). More eyes with high-risk PDR or worse (DRSS > 65) were enrolled in Protocol S study (~37%) compared to in the pooled RISE and RIDE studies (<2.0%) that were used for approval of ranibizumab for the treatment of DR in patients with DME.

Table 5: Summary of DR Severity Score at Baseline
(ITT Population)

	Protocol S Study						Pooled RISE and RIDE	
	PRP			Ranibizumab 0.5 mg PRN			Ranibizumab Monthly	
Baseline DRSS	Overall (N=203)	DME (N=46)	No DME (N=157)	Overall (N=191)	DME (N=42)	No DME (N=149)	0.5 mg (N=247)	0.3 mg (N=245)
Sever NPDR or Better (<= Level 53)	26 (12.8)	5 (10.9)	21 (13.4)	19 (10.0)	3 (7.1)	16 (10.7)	154 (31.6)	160 (65.3)
Mild-to-Moderate PDR (60, 61, 65)	99 (48.8)	21 (45.7)	78 (49.7)	98 (51.3)	17 (40.5)	81 (54.4)	71 (28.7)	78 (31.8)
60 (prior PRP; without active PDR)	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0	0
61A, 61B (mild PDR)	31 (15.3)	6 (13.0)	25 (15.9)	30 (15.7)	5 (11.9)	25 (16.8)	64 (26.1)	69 (27.9)
65A-65C (moderate PDR)	67 (33.0)	15 (32.6)	52 (33.1)	68 (35.6)	12 (28.6)	56 (37.6)	7 (2.9)	9 (3.6)
High-risk PDR or worse (DRSS > 65)	74 (36.5)	19 (41.3)	55 (35.0)	72 (37.7)	21 (50.0)	51 (34.2)	2 (0.8)	3 (1.2)
71A-71D (high-risk PDR)	53 (26.1)	15 (32.6)	38 (24.2)	47 (24.6)	13 (31.0)	34 (22.8)	3 (1.2)	1 (0.4)
75 (high-risk PDR)	20 (9.9)	4 (8.7)	16 (10.2)	22 (11.5)	8 (19.0)	14 (9.4)	0	1 (0.4)
81 (advanced PDR, macula center attached)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (1.3)	0	0
85 (advanced PDR, macula center detached)	1 (0.5)	0 (0.0)	1 (0.6)	1 (0.5)	0 (0.0)	1 (0.7)	0	0
90 (missing or cannot grade) ^[1]	4 (2.0)	1 (2.2)	3 (1.9)	2 (1.0)	1 (2.4)	1 (0.7)	13 (5.3)	11 (4.5)

^[1]Four eyes in the PRP group and two eyes in the ranibizumab group were excluded in the analyses of DR-related endpoints due to missing DRSS data at baseline.

Source: Table 4 of Applicant Summary of Clinical Efficacy and Table 3 of statistical review for RISE/RIDE Studies

Note: For the detailed summary of baseline DRSS, see Appendix Table 30 for Protocol S and Table 31 for RISE/RIDE studies.

Reviewer's Note:

Presence of PDR was one of the key inclusion criteria in the study; however, based on the data from the image reading center (see Table 5), 10% of eyes in the ranibizumab group and 13% of eye in the PRP group had NPDR or better at baseline. This inconsistency could be due to the study design as "study participant eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation)" (excerpts from protocol section 2.3.2.).

3.2.4 Efficacy Results and Conclusions

The results for the DR-related endpoints of proportion of eyes with ≥ 3 -step and ≥ 2 -step improvement, and with ≥ 3 -step and ≥ 2 -step worsening in DRSS from baseline at year 1 and year 2 are discussed in this section. The summary of the change in BCVA from baseline at each visit are also presented by treatment group.

DR-related outcomes were assessed in the study annually: at baseline, year 1, and year 2. The summary of the number of eyes with no DRSS data at these visits are shown in Table 6. About 18% of eyes at year 1 and 24% of eyes at year 2 did not have DRSS data due to early dropout, missing visit, or because images could not be graded. The rate of missing DRSS data at year 1 and year 2 was slightly higher in Protocol S study than in the pooled RISE/RIDE studies; for example about 15% and 20% of subjects in the pooled RISE/RIDE studies (without the sham group) had missing DRSS data at year 1 and year 2, respectively.

Table 6: Number of Eyes with Missing DRSS Data by Visit (ITT Population)

Visit	Reason for DRSS Missing	PRP (N = 203)	Ranibizumab (N = 191)	All (N = 394)
Baseline	Dropout	0	0	0
	Images could not be graded	4 (2.0%)	2 (1.0%)	6 (1.5%)
	Total	4 (2.0%)	2 (1.0%)	6 (1.5%)
Year 1	Dropout	11 (5.4%)	10 (5.2%)	21 (5.3%)
	Miss Visit/cannot be graded	26 (12.8%)	24 (12.6%)	50 (12.7%)
	Total ^[1]	37 (18.2%)	34 (17.8%)	71 (18.0%)
Year 2	Dropout	27 (13.3%)	28 (14.7%)	55 (14.0%)
	Miss Visit/ cannot be graded	19 (9.4%)	19 (9.9%)	38 (9.6%)
	Total ^[1]	46 (22.7%)	47 (24.6%)	93 (23.6%)

Based on reviewer analysis

^[1] 24 Eyes in the PRP group and 26 Eyes in the ranibizumab group had missing DRSS data at both Year 1 and Year 2 visits.

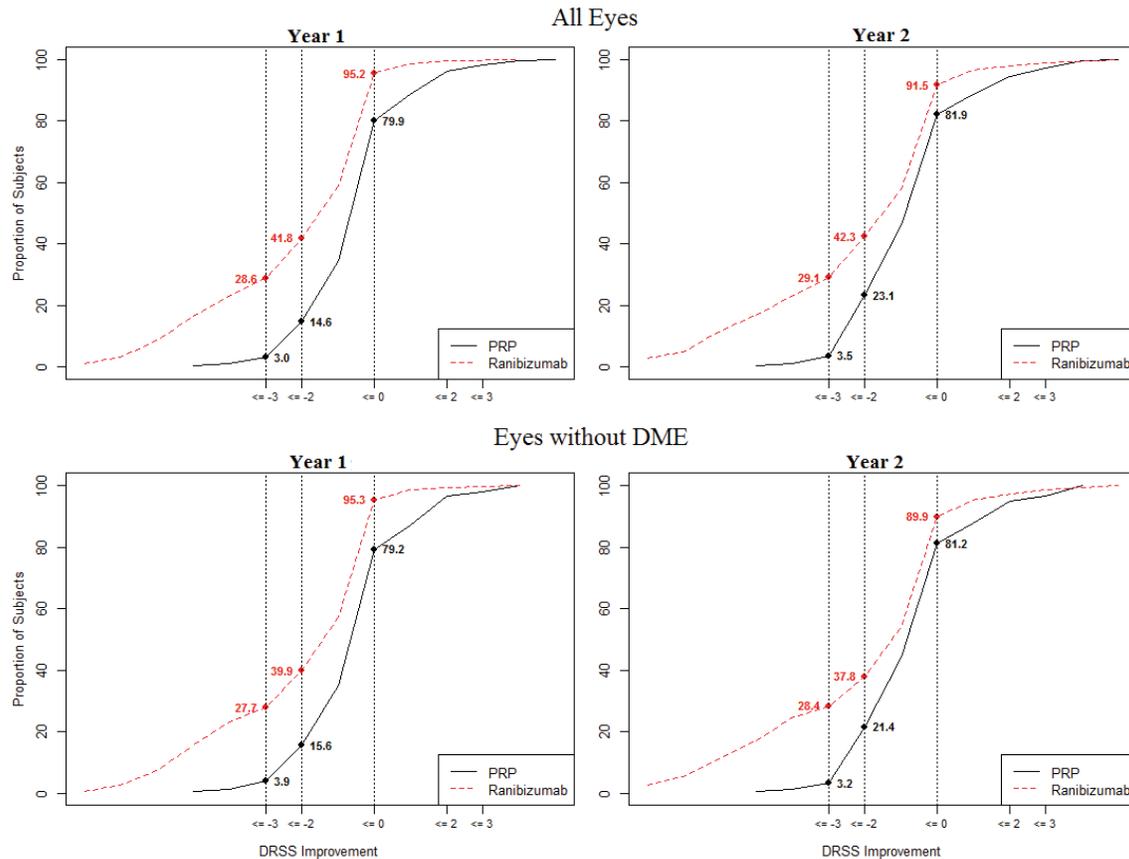
3.2.4.1 Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement in DRSS

The cumulative distribution of the change in DRSS from baseline at year 1 and year 2 are presented in Figure 4 for all eyes and for eyes without DME at baseline. In both cases, the eyes in the ranibizumab group demonstrated marked improvement in DRSS at year 1 and year 2 compared to the eyes in the PRP group.

At both time points, about 42% and 29% of all eyes in the ranibizumab group yielded ≥ 2 -step and ≥ 3 -step improvement in DRSS, respectively. In the PRP group, on the other hand, about 15% of all eyes at year 1 and 23% of all eyes at year 2 showed ≥ 2 -step improvement, and less than 4% of eyes at both visits showed ≥ 3 -step improvement.

The same pattern was seen in eyes without DME at baseline.

Figure 4: Cumulative Distribution of the Change in DRSS at Year 1 and Year 2 (mITT Population, LOCF)



The summary of the number and proportion of eyes with ≥ 2 -step and ≥ 3 -step improvement in DRSS from baseline at year 1 and year 2 are presented in [Table 7](#) and [Table 8](#). Summaries are provided for all eyes as well as by DME status at baseline (yes or no) and number of eyes enrolled per subject (one or two). In the overall eyes, about 27% and 26% more eyes in the ranibizumab group showed ≥ 2 -step and ≥ 3 -step improvement at year 1, respectively, than in the PRP group. Similarly, about 19% and 26% more eyes in the ranibizumab group showed ≥ 2 -step and ≥ 3 -step improvement at year 2, respectively, than in the PRP group.

In the ranibizumab group, a large percentage of eyes without DME at baseline demonstrated ≥ 2 - and ≥ 3 -step improvement. For example, about 40% of eyes at year 1 and 39% of eyes at year 2 yielded ≥ 2 -step improvement; and 28% of eyes showed ≥ 3 -step improvement at both visits. In this group, a slightly higher percentage of eyes with baseline DME than without DME had improvement in DRSS at both visits. See [section 3.2.4.3](#) and [Table 29](#) for comparison between the ranibizumab DME versus non-DME group.

In the PRP group, the proportion of eyes without DME at baseline that yielded ≥ 2 -step and ≥ 3 -step improvement was slightly lower than eyes in the ranibizumab group. For example, about 16% and 21% of eyes without DME at baseline showed ≥ 2 -step improvement at year 1 and year 2, respectively; and $< 4\%$ of eyes showed ≥ 3 -step improvement at both visits. In this group, none of the eyes with DME at baseline showed ≥ 3 -step improvement at year 1, and only one eye showed ≥ 3 -step improvement at year 2.

Table 7: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement in DRSS at Year 1 (mITT Population, LOCF)

Baseline DME	Number of Eyes	≥ 2 -Step Improvement			≥ 3 -Step Improvement		
		PRP (N=199) n/N (%)	Ranibizumab (N=189) n/N (%)	% Difference ^[1] (95% CI)	PRP (N=199) n/N (%)	Ranibizumab (N=189) n/N (%)	% Difference (95% CI) ^[1]
Yes	One	1/25 (4.0)	11/21 (52.4)		0/25 (0.0)	8/21 (38.1)	
	Two	4/20 (20.0)	9/20 (45.0)		0/20 (0.0)	5/20 (25.0)	
	Overall (95% CI) ^[2]	5/45 (11.1) (1.9, 20.3)	20/41 (48.8) (33.5, 64.1)	37.7 (19.8, 55.5)	0/45 (0.0)	13/41 (31.7) (17.5, 46.0)	
No	One	14/88 (15.9)	37/80 (46.3)		5/88 (5.7)	24/80 (30.0)	
	Two	10/66 (15.2)	22/68 (32.4)		1/66 (1.5)	17/68 (25.0)	
	Overall (95% CI) ^[2]	24/154 (15.6) (9.9, 21.3)	59/148 (39.9) (32.0, 47.8)	24.3 (14.5, 34.0)	6/154 (3.9) (0.8, 7.0)	41/148 (27.7) (20.5, 34.9)	23.8 (16.0, 31.6)
Overall	Overall (Un-adjusted) (95% CI) ^[2]	29/199 (14.6) (9.7, 19.5)	79/189 (41.8) (34.8, 48.8)	27.2 (18.7, 35.8)	6/199 (3.0) (0.6, 5.4)	54/189 (28.6) (22.1, 35.0)	25.6 (18.7, 32.4)
	Overall (Adjusted) (95% CI) ^[1]	14.7 (9.8, 19.6)	42.0 (35.1, 49.0)	27.4 (18.9, 35.9)	3.0 (0.7, 5.3)	28.7 (22.3, 35.1)	25.7 (18.9, 32.6)

Table 8: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement in DRSS at Year 2 (mITT Population, LOCF)

Baseline DME	Number of Eyes	≥ 2 -Step Improvement			≥ 3 -Step Improvement		
		PRP (N=199) n/N (%)	Ranibizumab (N=189) n/N (%)	Difference ^[1] (95% CI)	PRP (N=199) n/N (%)	Ranibizumab (N=189) n/N (%)	Difference (95% CI) ^[1]
Yes	One	5/25 (20.0)	11/21 (52.4)		1/25 (4.0)	6/21 (28.6)	
	Two	8/20 (40.0)	13/20 (65.0)		1/20 (5.0)	7/20 (35.0)	
	Overall (95% CI) ^[2]	13/45 (28.9) (15.6, 42.1)	24/41 (58.5) (43.5, 73.6)	29.6 (9.6, 49.7)	2/45 (4.4) (-1.6, 10.5)	13/41 (31.7) (17.5, 46.0)	27.3 (11.8, 42.7)
No	One	18/88 (20.5)	37/80 (46.3)		4/88 (4.5)	27/80 (33.8)	
	Two	15/66 (22.7)	19/68 (27.9)		1/66 (1.5)	15/68 (22.1)	
	Overall (95% CI) ^[2]	33/154 (21.4) (14.9, 27.9)	56/148 (37.8) (30.0, 45.7)	16.4 (6.3, 26.6)	5/154 (3.2) (0.4, 6.0)	42/148 (28.4) (21.1, 35.6)	25.1 (17.3, 32.9)
Overall	Overall (Un-adjusted) (95% CI) ^[2]	46/199 (23.1) (17.3, 29.0)	80/189 (42.3) (35.3, 49.4)	19.2 (10.1, 28.4)	7/199 (3.5) (1.0, 6.1)	55/189 (29.1) (22.6, 35.6)	25.6 (18.6, 32.5)
	Overall (Adjusted) (95% CI) ^[1]	23.2 (17.4, 29.0)	42.6 (35.7, 49.4)	19.4 (10.4, 28.4)	3.5 (1.0, 6.0)	29.2 (22.8, 35.7)	25.7 (18.8, 32.7)

^[1] Adjusted: Difference with confidence interval (CI) based on CMH weighting scheme adjusted for baseline DME status and number of eyes enrolled

^[2] Un-adjusted: Difference with confidence interval (CI) based on binomial distribution for normal approximation

Overall, in all eyes as well as in the subgroup of eyes with and without DME at baseline, treatment with ranibizumab demonstrated superior improvement in DRSS to treatment with PRP. However, it is unclear if the low rate of improvement in the PRP group was due to lack of treatment effect or because the majority of eyes in the PRP group could not achieve ≥ 2 -step and/or ≥ 3 -step improvement due to the nature of the grading scheme resulting from PRP-induced scars.

DRSS Grading Scheme in PRP-treated Eyes

In Protocol S study, fundus images of PRP-treated eyes with a definite presence of scars received a minimum DRSS score of 60: DRSS score of 60 was assigned to images with definite PRP scars if PDR was inactive and DRSS >60 was assigned if presence of PDR was detected. In few cases, DRSS < 60 was also assigned because scars resulting from PRP could not be conclusively confirmed. Accordingly, fundus images of all PRP-treated eyes in the study received DRSS score ≥ 60 except for three patients in the PRP group that received DRSS < 60 at year 1 or year 2 (See Table 9 below).

Table 9: PRP-treated Eyes with DRSS ≤ 65 at Baseline and DRSS <60 at Year 1 or Year 2 (mITT Population, LOCF)

Patient ID	Baseline DME	Study Eye	DRSS		
			Baseline	Year 1	Year 2
(b) (6)	No	One	47A	35D	60
	No	Two	35B	35C	60
	No	Two	61B	35C	35C

Due to the nature of the DRSS grading scheme, the majority of eyes in the PRP group with baseline DRSS ≤ 65 (or DRSS ≤ 71) could not achieve ≥ 2 -step (or ≥ 3 -step) improvement from baseline. For example, in the PRP group, 62.8% of eyes (or 89.5% of eyes) with baseline DRSS ≤ 65 (or DRSS ≤ 71) could not achieve ≥ 2 -step (or ≥ 3 -step) improvement. Also, a small number of eyes (13 eyes) in the ranibizumab group that received PRP during the study had similar situation, but the impact of these eyes on the overall result was minimal unlike in the PRP group.

Therefore, in the sBLA, a meaningful and interpretable head-to-head treatment comparison based on all eyes could not be made under this circumstance. However, a potentially meaningful and interpretable treatment comparison could be made in the subgroup of eyes with baseline DRSS > 65 (or DRSS > 71) since in these subgroups PRP-treated eyes could achieve ≥ 2 -step (or ≥ 3 -step) improvement irrespective of presence of scars.

3.2.4.2 Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement by Baseline DRSS

The summary of the number and proportion of eyes with ≥ 2 -step and ≥ 3 -step improvement in DRSS at year 1 and year 2 are presented in Table 10 and Table 11 by baseline DRSS categories. In the baseline DRSS categories where the PRP group could potentially achieve improvement (*i.e.*, DRSS >65 for ≥ 2 -step improvement and DRSS >71 for ≥ 3 -step improvement), eyes in the PRP group appeared to display increased improvement than what was seen in the overall population.

Table 10: Proportion of Eyes with ≥ 2 -Step Improvement in DRSS by Baseline DRSS (mITT Population, LOCF)

Visit	Baseline DRSS Category	PRP			Ramibizumab (N=189) % (n/N)	% Difference (95% CI)	95% Bootstrap CI	p-value ^[1]
		With ramibizumab (N=109)	Without ramibizumab (N = 90)	Overall (N = 199)				
Year 1	Overall	19.3 (21/109)	8.9 (8/ 90)	14.6 (29/199)	41.8 (79/189)	27.4 (18.9, 35.9)	(20.9, 39.3)	<0.0001
	Moderate PDR or Better (≤ 65)	1.6 (1/ 63)	1.6 (1/ 62)	1.6 (2/125)	30.8 (36/117)	30.0 (21.2, 38.9)	(21.9, 40.9)	
	High-risk PDR or worse (> 65)	43.5 (20/ 46)	25.0 (7/ 28)	36.5 (27/ 74)	59.7 (43/ 72)	22.7 (7.1, 38.4)	(12.5, 46.5)	0.0021
	High-risk PDR (71A - 71D)	41.2 (14/ 34)	26.3 (5/ 19)	35.8 (19/ 53)	59.6 (28/ 47)	23.6 (4.5, 42.8)	(2.7, 47.6)	
Year 2	High-risk PDR or worse (>71)	50.0 (6/ 12)	22.2 (2/ 9)	38.1 (8/ 21)	60.0 (15/ 25)	21.7 (-4.4, 47.7)	(5.8, 68.3)	
	Overall	27.5 (30/109)	17.8 (16/ 90)	23.1 (46/199)	42.3 (80/189)	19.4 (10.4, 28.4)	(10.1, 27.3)	<0.0001
	Moderate PDR or Better (≤ 65)	0.0 (0/ 63)	1.6 (1/ 62)	0.8 (1/125)	31.6 (37/117)	32.0 (23.3, 40.6)	(23.1, 40.6)	
	High-risk PDR or worse (> 65)	65.2 (30/ 46)	53.6 (15/ 28)	60.8 (45/ 74)	59.7 (43/ 72)	-1.8 (-17.4, 13.7)	(-16.0, 13.8)	0.7266
	High-risk PDR (71A - 71D)	64.7 (22/ 34)	68.4 (13/ 19)	66.0 (35/ 53)	61.7 (29/ 47)	-4.9 (-23.8, 14.0)	(-23.4, 12.8)	
	High-risk PDR or worse (>71)	66.7 (8/ 12)	22.2 (2/ 9)	47.6 (10/ 21)	56.0 (14/ 25)	-1.4 (-30.7, 27.9)	(-44.2, 46.6)	

Table 11: Proportion of Eyes with ≥ 3 -Step Improvement in DRSS by Baseline DRSS (mITT Population, LOCF)

Visit	Baseline DRSS Category	PRP			Ramibizumab (N=189) % (n/N)	% Difference (95% CI)	95% Bootstrap CI	p-value ^[1]
		With ramibizumab (N=109)	Without ramibizumab (N = 90)	Overall (N = 199)				
Year 1	Overall	3.7 (4/109)	2.2 (2/ 90)	3.0 (6/199)	28.6 (54/189)	25.7 (18.9, 32.6)	(19.4, 33.3)	<0.0001
	Moderate PDR or Better (≤ 65)	0.0 (0/ 63)	1.6 (1/ 62)	0.8 (1/125)	24.8 (29/117)	24.3 (16.2, 32.5)	(17.3, 32.6)	
	High-risk PDR or worse (> 65)	8.7 (4/ 46)	3.6 (1/ 28)	6.8 (5/ 74)	34.7 (25/ 72)	26.8 (14.2, 39.5)	(14.4, 39.2)	
	High-risk PDR (71A - 71D)	0.0 (0/ 34)	0.0 (0/ 19)	0.0 (0/ 53)	31.9 (15/ 47)	32.1 (18.7, 45.6)	(18.7, 45.1)	
Year 2	High-risk PDR or worse (>71)	33.3 (4/ 12)	11.1 (1/ 9)	23.8 (5/ 21)	40.0 (10/ 25)	13.4 (-8.8, 35.5)	(-15.5, 44.4)	0.2912
	Overall	4.6 (5/109)	2.2 (2/ 90)	3.5 (7/199)	29.1 (55/189)	25.7 (18.8, 32.7)	(18.7, 31.8)	<0.0001
	Moderate PDR or Better (≤ 65)	0.0 (0/ 63)	1.6 (1/ 62)	0.8 (1/125)	25.6 (30/117)	25.7 (17.5, 33.9)	(18.0, 33.9)	
	High-risk PDR or worse (> 65)	10.9 (5/ 46)	3.6 (1/ 28)	8.1 (6/ 74)	34.7 (25/ 72)	26.2 (13.1, 39.2)	(13.5, 38.9)	
	High-risk PDR (71A - 71D)	0.0 (0/ 34)	0.0 (0/ 19)	0.0 (0/ 53)	34.0 (16/ 47)	34.0 (20.4, 47.6)	(20.7, 46.8)	
	High-risk PDR or worse (>71)	41.7 (5/ 12)	11.1 (1/ 9)	28.6 (6/ 21)	36.0 (9/ 25)	2.5 (-21.9, 26.9)	(-26.9, 32.3)	1.0000

[1] P-values are from generalized estimating equations (GEE) model accounting for the correlation within study participants with two study eyes.

For example, at year 1 and year 2, respectively, about 37% (27/74) and 61% (45/74) of eyes in the PRP group with baseline DRSS > 65 yielded ≥ 2 -step improvement compared to 15% (29/199) and 23% (45/199) of eyes in the overall population; and about 24% (5/21) and 29% (6/21) of eyes with baseline DRSS > 71 yielded ≥ 3 -step improvement compared to 3% (6/199) and 4% (7/199) of eyes in the overall population. It is worth noting that almost all the DRSS improvement seen in the overall population in the PRP group was from eyes with baseline DRSS > 65 (or DRSS > 71) for the ≥ 2 -step (or ≥ 3 -step) improvement.

The eyes in the Ranibizumab group also displayed increased improvement in these subgroups of eyes compared to what was seen in the overall population. For example, at year 1 and year 2, about 60% of eyes with baseline DRSS>65 showed at least ≥ 2 -step improvement compared to 42% of eyes in the overall population; and 40% and 36% of eyes with baseline DRSS>71 yielded ≥ 3 -step improvement at year 1 and year 2, respectively, compared to 29% of eyes in the overall population at both time points.

In eyes with baseline DRSS > 65, the ranibizumab group was statistically superior to the PRP group in the proportion of eyes with ≥ 2 -step improvement at year 1 but was numerically lower than the PRP group at year 2; the treatment difference (*ranibizumab minus PRP*) at year 1 was **23% (95% CI: 7%, 38%)** and at year 2 was **-2% (95% CI: -17%, 14%)**.

In eyes with baseline DRSS>71, the ranibizumab group showed numerical advantage in the proportion of eyes with ≥ 3 -step improvement at both time points but the treatment difference was not statistically significant: the treatment difference at year 1 was **13% (95% CI: -9%, 36%)** and at year 2 was **3% (95% CI: -22%, 27%)**.

The lack of statistically significant difference (*at year 1 for ≥ 2 -step improvement and at both time points for ≥ 3 -step improvement*) could be due to the ranibizumab injection a slight majority of eyes in the PRP group (~54%) had received during the 2-years treatment period and/or likely due to the small number of eyes with baseline DRSS > 65 enrolled in the study.

Regarding the ranibizumab injection, 110 eyes in the PRP group received a total of 687 ranibizumab injections during the 2 years treatment period (Mean = 6.3; range: 1 – 20); and 46 of these eyes had baseline DRSS > 65 and received 283 of the total 687 injections (See [Table 12](#) below). Therefore, the efficacy results in the PRP group may have been confounded by the ranibizumab injection received during the study.

Table 12: Summary of Ranibizumab Injection Eyes in the PRP group Received During the Study

Baseline DRSS	N (%)	Ranibizumab Injection Summary			
		Total	Mean (SD)	Median	Range
Overall	110 (100%)	687 (100%)	6.3 (5.15)	5.0	1-20
Sever NPDR or better (DRSS <60)	14 (12.7%)	100 (14.5%)	7.1 (6.04)	6.0	1-20
Mild PDR (DRSS = 61)	14 (12.7%)	78 (11.4%)	5.6 (4.57)	5.5	1-18
Moderate PDR (DRSS = 65)	35 (31.8%)	217 (31.6%)	6.2 (5.13)	5.0	1-18
High Risk PDR or worse (DRSS >65)	46 (41.8%)	283 (41.2%)	6.2 (5.22)	5.0	1-20
Missing/could not be graded	1 (0.9%)	9 (1.3%)	9.0 (NA)	9.0	9-9

To assess the potential confounding effect, the efficacy results in the PRP group were presented for eyes with and without ranibizumab injection (See [Table 10](#) and [Table 11](#) above). Evidently, more eyes in the PRP group that received the ranibizumab injection during the study demonstrated better

improvement in DRSS than eyes without the injection. For example at year 2, 65% (42%) of eyes in the PRP group with baseline DRSS > 65 (DRSS >71) that received ranibizumab injection achieved ≥ 2 -step (≥ 3 -step) improvement compared to 54% (11%) of eyes without the injection. See Appendix Table 26 for the treatment comparison between eyes in the PRP group without the ranibizumab injection versus eyes in the ranibizumab group. The results by baseline DME status are shown in Table 13 below.

Table 13: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement by DME Status (mITT Population, LOCF)

DME Status	Visit	PRP with Ranibizumab	PRP without Ranibizumab	Overall PRP % (n/N)	Ranibizumab % (n/N)	Difference (95% CI) ^[1]
≥ 2-Step Improvement: Baseline DRSS > 65						
Yes	Year 1	26.3 (5/ 19)	--	26.3 (5/ 19)	61.9 (13/21)	35.6 (6.9, 64.3)
	Year 2	68.4 (13/ 19)	--	68.4 (13/ 19)	76.2 (16/ 21)	7.8 (-20.0, 35.5)
No	Year 1	55.6 (15/ 27)	25.0 (7/ 28)	40.0 (22/ 55)	58.8 (30/ 51)	18.8 (0.1, 37.5)
	Year 2	63.0 (17/ 27)	53.6 (15/ 28)	58.2 (32/ 55)	52.9 (27/ 51)	-5.2 (-24.2, 13.7)
Overall	Year 1	43.5 (20/ 46)	25.0 (7/ 28)	36.5 (27/ 74)	59.7 (43/ 72)	22.7 (7.1, 38.4)
	Year 2	65.2 (30/ 46)	53.6 (15/ 28)	60.8 (45/ 74)	59.7 (43/ 72)	-1.8 (-17.4, 13.7)
≥ 3-Step Improvement: Baseline DRSS > 71						
Yes	Year 1	0.0 (0/ 4)	--	0.0 (0/ 4)	62.5 (5/ 8)	62.5 (29.0, 96.0)
	Year 2	50.0 (2/ 4)	--	50.0 (2/ 4)	62.5 (5/ 8)	12.5 (-46.9, 71.9)
No	Year 1	50.0 (4/ 8)	11.1 (1/ 9)	29.4 (5/ 17)	29.4 (5/ 17)	0.0 (-30.6, 30.6)
	Year 2	37.5 (3/ 8)	11.1 (1/ 9)	23.5 (4/ 17)	23.5 (4/ 17)	0.0 (-28.5, 28.5)
Overall	Year 1	33.3 (4/ 12)	11.1 (1/ 9)	23.8 (5/ 21)	40.0 (10/ 25)	13.4 (-8.8, 35.5)
	Year 2	41.7 (5/ 12)	11.1 (1/ 9)	28.6 (6/ 21)	36.0 (9/ 25)	2.5 (-21.9, 26.9)

^[1] Difference with confidence interval (CI) based on binomial distribution for normal approximation

In summary, in the subgroup of eyes where meaningful head-to-head treatment comparison could be made; treatment with ranibizumab injection still displayed numerically greater improvement in DRSS than treatment with PRP. The treatment benefit with ranibizumab injection was further demonstrated in the eyes in the PRP group that received ranibizumab injection during the study.

3.2.4.3 Efficacy Results: Ranibizumab with DME versus without DME at Baseline

The proportion of eyes with ≥ 2 -step and ≥ 3 -step improvement in DRSS at year 1 and year 2 for eyes in the ranibizumab group with and without DME at baseline were summarized in Table 14. The analyses by baseline DRSS categories were summarized in Appendix Table 29.

Table 14: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement: Ranibizumab Group with DME versus without DME at Baseline (mITT Population; LOCF)

	Visit	No DME (N=148) % (95 % CI)	DME (N=41) % (95 % CI)	Difference (95% CI)
≥ 2 -Step Improvement	Year 1	39.9 (32.0, 47.8)	48.8 (33.5, 64.1)	8.9 (-8.3, 26.1)
	Year 2	37.8 (30.0, 45.7)	58.5 (43.5, 73.6)	20.7 (3.7, 37.7)
≥ 3 -Step Improvement	Year 1	27.7 (20.5, 34.9)	31.7 (17.5, 46.0)	4.0 (-12.0, 20.0)
	Year 2	28.4 (21.1, 35.6)	31.7 (17.5, 46.0)	3.3 (-12.7, 19.3)

Overall, the two groups were comparable in the proportion of eyes with ≥ 3 -step improvement at year 1 and year 2; however, the proportion of eyes with ≥ 2 step improvement was numerically higher in eyes with DME than without DME. This may be likely because more eyes with DME had high-risk PDR or worse at baseline than eyes without DME (See Table 5) and/or likely due to the difference in the number of ranibizumab injection received in these groups; note that eyes with DME received on average 2 more injections prior to year 1 and 3 more injection prior to year 2 than eyes without DME (See Table 22).

3.2.4.4 Sensitivity Analyses

During the 2-years treatment period, 18% and 24% of eyes in both treatment groups had missing DRSS data at year 1 and year 2, respectively (See Table 6); 5% of eyes at year 1 and 14% of eyes at year 2 had missing data due to early dropout, and 13% of eyes at year 1 and 10% of eyes at year 2 had missing data due to missing visit or because images could not be graded. In the applicant primary analysis, missing data were imputed using the last available gradable DRSS data (including gradable baseline DRSS data). The applicant performed sensitivity analyses using observed cases (without missing data imputation) and using Markov Chain Monte Carlo multiple imputation (MI) for handling missing data to assess the robustness of the efficacy results (See Table 15 below).

The reviewer also performed two additional sensitivity analyses: (i) treating eyes with missing data as non-responders and (ii) MI using the sham rate for the proportion of subjects with ≥ 2 -step (or ≥ 3 -step) improvement observed in the pooled RISE/RIDE studies to derive the imputation. In the MI approach, missing responder or non-responder status were generated from Bernoulli distribution using sham success rate of 2.5% at year 1 and 5.4% at year 2 for ≥ 2 -step improvement and 1.3% at both time points for ≥ 3 -step improvement. In each case 20 datasets were generated and the results from each dataset were combined using PROC MIANALYZE. The efficacy results based on the two missing data imputation approaches were comparable. Overall, the conclusions from the sensitivity analyses were consistent with the LOCF method used in the primary analyses except for small numerical differences.

Table 15: Sensitivity Analyses: Efficacy Results for the Ranibizumab Group Only by DME Status:

		Year 1			Year 2		
		Overall	DME	No DME	Overall	DME	No DME
LOCF	N	199	41	148	199	41	148
	≥ 2 -Step	41.8 (34.8, 48.8)	48.8 (33.5, 64.1)	39.9 (32.0, 47.8)	42.3 (35.3, 49.4)	58.5 (43.5, 73.6)	37.8 (30.0, 45.7)
	≥ 3 -Step	28.7 (22.3, 35.1)	32.0 (17.8, 46.2)	27.8 (20.6, 35.0)	29.2 (22.8, 35.7)	31.6 (17.4, 45.8)	28.6 (21.3, 35.8)
Observed	N	155	33	122	143	27	116
	≥ 2 -Step	51.0 (43.1, 58.8)	60.6 (43.9, 77.3)	48.4 (39.5, 57.2)	46.9 (38.7, 55.0)	66.7 (48.9, 84.4)	42.2 (33.3, 51.2)
	≥ 3 -Step	34.8 (27.3, 42.3)	39.4 (22.7, 56.1)	33.6 (25.2, 42.0)	33.6 (25.8, 41.3)	37.0 (18.8, 55.3)	32.8 (24.2, 41.3)
NR ^[1]	N	199	41	148	199	41	148
	≥ 2 -Step	41.8 (34.8, 48.8)	48.8 (33.5, 64.1)	39.9 (32.0, 47.8)	35.4 (28.6, 42.3)	43.9 (28.7, 59.1)	33.1 (25.5, 40.7)
	≥ 3 -Step	28.6 (22.1, 35.0)	31.7 (17.5, 46.0)	27.7 (20.5, 34.9)	25.4 (19.2, 31.6)	24.4 (11.2, 37.5)	25.7 (18.6, 32.7)
MI ^[2]	N	199	41	148	199	41	148
	≥ 2 -Step	53.7 (46.1, 61.4)	61.1 (44.7, 77.5)	51.7 (43.2, 60.2)	50.6 (43.0, 58.2)	66.3 (49.4, 83.3)	46.2 (37.5, 54.9)
	≥ 3 -Step	37.6 (30.2, 45.0)	40.6 (23.8, 57.4)	36.8 (28.4, 45.1)	36.2 (28.6, 43.9)	40.2 (22.9, 57.6)	35.1 (26.9, 43.4)
MI ^[3]	N	199	41	148	199	41	148
	≥ 2 -Step	42.2 (35.1, 49.3)	49.3 (33.8, 64.7)	40.3 (32.3, 48.2)	36.5 (29.4, 43.5)	45.5 (29.5, 61.5)	34.0 (26.2, 41.7)
	≥ 3 -Step	28.8 (22.3, 35.2)	31.8 (17.5, 46.1)	27.9 (20.6, 35.2)	25.7 (19.4, 32.0)	24.9 (11.4, 38.4)	25.9 (18.8, 33.0)

^[1] Eyes with missing DRSS data treated as non-responders (NR);

^[2] Multiple imputation based on Applicant analyses (Source: Clinical Summary of Efficacy); ^[3] Multiple Imputation derived by sham rate (Reviewer Analyses).

3.2.4.5 Analyses of Other Efficacy Variables

(i) Proportion of eyes with ≥ 2 -step or ≥ 3 -step worsening

The proportions of eyes with ≥ 2 -step or ≥ 3 -step worsening from baseline at year 1 and year 2 are shown in Table 16 below by treatment group and baseline DRSS categories.

Table 16: Proportion of Eyes with ≥ 2 -Step or ≥ 3 -Step Worsening in DRSS (mITT Population, LOCF)

Visit	Baseline DRSS Categories	≥ 2 -step worsening		≥ 3 -step worsening	
		PRP % (n/N)	Ranibizumab % (n/N)	PRP % (n/N)	Ranibizumab % (n/N)
Year 1	Overall	11.6 (23/199)	1.6 (3/189)	4.0 (8/199)	0.5 (1/189)
	DRSS ≤ 47	76.0 (19/ 25) ^[1]	11.1 (2/ 18)	32.0 (8/ 25) ^[2]	5.6 (1/ 18)
	DRSS > 47	2.3 (4/174)	0.6 (1/171)	0.0 (0/174)	0.0 (0/171)
Year 2	Overall	11.6 (23/199)	3.7 (7/189)	5.5 (11/199)	2.1 (4/189)
	DRSS ≤ 47	88.0 (22/ 25) ^[3]	16.7 (3/ 18)	40.0 (10/ 25) ^[4]	11.1 (2/ 18)
	DRSS > 47	0.6 (1/174)	2.3 (4/171)	0.6 (1/174)	1.2 (2/171)

^[1] 16 of 19 eyes were assigned DRSS=60 while 3 of 19 eyes were assigned DRSS=61; ^[2] 8 of 8 eyes were assigned DRSS=60

^[3] 20 of 22 eyes were assigned DRSS=60 while 2 of 22 eyes were assigned DRSS>60; ^[4] 8 of 10 eyes were assigned DRSS=60

It appeared that more eyes in the PRP group had worsening in DR severity than in the ranibizumab group at both time points. In the PRP group, almost all the worsening reported in the overall summary was from eyes with moderately severe NPDR or better at baseline (DRSS ≤ 47); note that, the majority of these eyes were assigned DRSS ≥ 60 at year 1 and year 2 due to the presence of definite scars.

(ii) Summary of Change in DRSS from Baseline at Year 1 and Year 2

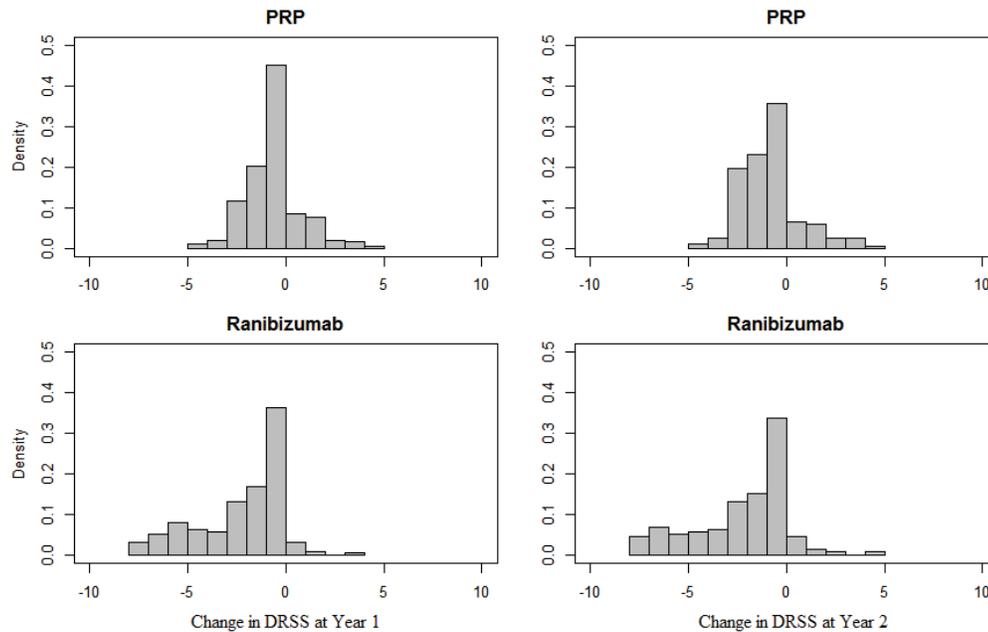
The summary of the change in DRSS from baseline at year 1 and year 2 are shown in Table 17 by treatment group and by baseline DRSS categories. The distribution of the change in DRSS at year 1 and year 2 are shown in Figure 5 by treatment group.

Overall, eyes in the ranibizumab group demonstrated about 2-unit improvement on average while eyes in the PRP group demonstrated $< 1/2$ -unit. In eyes with high-risk PDR or worse at baseline (DRSS > 65), both treatment group yielded a median improvement of about 2-unit at year 2.

Table 17: Summary of Change in DRSS from Baseline by Baseline DRSS (mITT population; LOCF)

Visit	Baseline DRSS	PRP				Ranibizumab			
		N	Mean (SD)	Median	Percentiles (2.5%, 97.5%)	N	Mean (SD)	Median	Percentiles (2.5%, 97.5%)
Year 1	Overall	199	-0.2 (1.40)	0	(-3.0, 3.0)	189	-1.7 (2.24)	-1	(-7.0, 1.0)
	DRSS ≤ 65	125	0.3 (1.32)	0	(-1.0, 4.0)	117	-1.4 (2.06)	-1	(-6.0, 1.0)
	DRSS > 65	74	-1.0 (1.15)	-1	(-3.0, 1.0)	72	-2.3 (2.40)	-2	(-8.0, 0.0)
	DRSS = 71	53	-0.9 (0.95)	-1	(-2.0, 1.0)	47	-2.6 (2.65)	-2	(-8.0, 0.0)
	DRSS > 71	21	-1.1 (1.56)	0	(-5.0, 1.0)	25	-2.0 (1.81)	-2	(-7.0, 0.0)
Year 2	Overall	199	-0.4 (1.55)	0	(-3.0, 4.0)	189	-1.7 (2.51)	-1	(-8.0, 2.0)
	DRSS ≤ 65	125	0.3 (1.40)	0	(-1.0, 4.0)	117	-1.2 (2.30)	0	(-6.0, 3.0)
	DRSS > 65	74	-1.4 (1.15)	-2	(-3.0, 0.0)	72	-2.5 (2.65)	-2	(-8.0, 1.0)
	DRSS = 71	53	-1.4 (1.04)	-2	(-2.0, 0.0)	47	-2.8 (2.98)	-2	(-8.0, 1.0)
	DRSS > 71	21	-1.6 (1.40)	-1	(-5.0, 0.0)	25	-1.9 (1.81)	-2	(-8.0, 0.0)

Figure 5: Distribution of the Change in DRSS at Year 1 and Year 2 (All Eyes)
(mITT population; LOCF)



(iii) Proportion of eyes with ≥ 2 -step improvement in DRSS from PDR at baseline to NPDR

The summary of the proportion of eyes with ≥ 2 -step improvement in DRSS from PDR at baseline to NPDR at year 1 and year 2 are presented in Table 18 by treatment group. In the ranibizumab group, 48 eyes at year 1 and 46 eyes at year 2 out of the total 170 eyes with PDR or worse at baseline (DRSS ≥ 60) had ≥ 2 -step improvement and achieved NPDR status. In the PRP group, on the other hand, only one eye out of the total 173 eyes with PDR or worse at baseline had ≥ 2 -step improvement and achieved NPDR status. This is again due to the nature of the DRSS grading scheme.

Table 18: Proportion of Eyes with ≥ 2 -Step Improvement from PDR at Baseline to NPDR
(mITT Population, LOCF)

	PRP Group			Ranibizumab Group		
	Overall (N=173)	No DME (N=133)	DME (N=40)	Overall (N=170)	No DME (N=132)	DME (N=38)
Year 1	1 (0.6%) (0.0%, 3.2%)	1 (0.8%) (0.0%, 4.1%)	0	48 (28.2%) (22.0%, 35.4%)	38 (28.8%) (21.8%, 37.0%)	10 (26.3%) (15.0%, 42.0%)
Year 2	1 (0.6%) (0.0%, 3.2%)	1 (0.8%) (0.0%, 4.1%)	0	46 (27.1%) (20.9%, 34.2%)	37 (28.0%) (21.1%, 36.2%)	9 (23.7%) (13.0%, 39.2%)

(iv) Analysis of Change in BCVA

The summary of the change in BCVA from baseline at each study visit is presented in Table 19 by baseline DME status and in Table 20 by the ranibizumab injection eyes in the PRP group received. At baseline, the mean BCVA in all eyes as well as in eyes with or without DME was comparable between the treatment groups. In both treatment groups, eyes with DME at baseline had a much lower mean baseline BCVA than eyes without DME.

Overall, the eyes in the ranibizumab group gained at least +3 more letters on average than in the PRP group throughout the study.

Table 19: Mean Change in BCVA from Baseline at Each Visit
(mITT Population, LOCF)

Visit	PRP			Ranibizumab		
	Overall (N=203)	No DME (N=157)	DME (N=46)	Overall (N=191)	No DME (N=149)	DME (N=42)
Baseline	75.2 (12.47)	78.3 (10.49)	64.7 (13.04)	75.0 (12.79)	78.1 (10.47)	63.8 (14.12)
Week 16	-1.3 (12.53)	-2.7 (12.48)	3.7 (11.52)	5.1 (8.99)	4.0 (7.17)	8.9 (13.05)
Week 32	-0.4 (14.44)	-2.0 (13.85)	5.2 (15.18)	6.1 (10.46)	4.5 (10.09)	11.5 (10.00)
Week 52 (Year 1)	-2.0 (19.01)	-3.8 (19.35)	4.2 (16.54)	5.8 (11.19)	4.4 (10.55)	11.0 (12.00)
Week 68	-3.1 (19.48)	-4.4 (19.30)	1.4 (19.65)	5.5 (12.14)	3.9 (11.68)	11.4 (12.04)
Week 84	-1.4 (17.98)	-2.6 (17.50)	3.0 (19.08)	4.8 (12.35)	3.2 (11.65)	10.1 (13.34)
Week 104 (Year 2)	-0.7 (15.45)	-1.2 (14.13)	1.2 (19.37)	2.7 (17.75)	0.8 (18.38)	9.3 (13.56)
Difference vs PRP						
Week 16				6.3 (4.9, 7.7)	6.7 (4.5, 9.0)	4.9 (0.1, 9.6)
Week 32				6.3 (4.7, 7.9)	6.4 (3.8, 9.1)	5.9 (1.4, 10.4)
Week 52 (Year 1)				7.7 (5.7, 9.8)	8.1 (4.7, 11.5)	6.3 (1.0, 11.6)
Week 68				8.5 (6.3, 10.6)	8.2 (4.6, 11.7)	9.5 (3.4, 15.6)
Week 84				6.0 (4.0, 8.1)	5.8 (2.5, 9.1)	6.6 (0.5, 12.8)
Week 104 (Year 2)				3.3 (1.0, 5.5)	1.9 (-1.6, 5.5)	7.8 (1.0, 14.7)

⁽¹⁾ Difference (versus PRP) with confidence interval (CI) was based on analysis of variance (ANOVA) model with treatment as the main effect and baseline BCVA as covariate.

In eyes with DME at baseline, the average number of letters gained in the ranibizumab group was significantly better than in the PRP group throughout the study. This was likely due to the difference in the number of ranibizumab injection received in these groups: the eyes in the PRP DME group received 8.1 injections (range: 1-20) on average compared to 12.4 injections (range: 5 – 22) the eyes in the ranibizumab DME group received prior to 2 years.

It is worth noting that the average number of letters eyes in the ranibizumab DME group gained at year 1 (+11.0) and year 2 (+9.3 letters) in Protocol S study was comparable to the ranibizumab DME subjects gained in the RISE/RIDE studies. In the pooled RISE/RIDE studies, the average number of letters gained was +10.6 in the 0.3 mg and +11.1 in the 0.5 mg at year 1 and was +11.7 in the 0.3 mg and +12.0 in the 0.5 mg at year 2. The average number of letters gained at year 2 was slightly higher in the pooled RISE/RIDE studies than in Protocol S study. This was likely because the subjects in the RISE/RIDE studies had lower mean baseline BCVA (about 57 letters) compared to the DME group in Protocol S study (about 64 letters) or due to the difference in the number of ranibizumab injection received during the 2 years.

In eyes with no DME at baseline, eyes in the PRP group on the average lost at least 1 letter throughout the study while eyes in the ranibizumab group gained at least +1 letter during the study. In the PRP group, the gain in visual acuity in eyes with no DME at baseline was very similar regardless of ranibizumab injection.

Table 20: Mean Change in BCVA for Eyes in the PRP Group with and without Ranibizumab Injection
(mITT Population, LOCF)

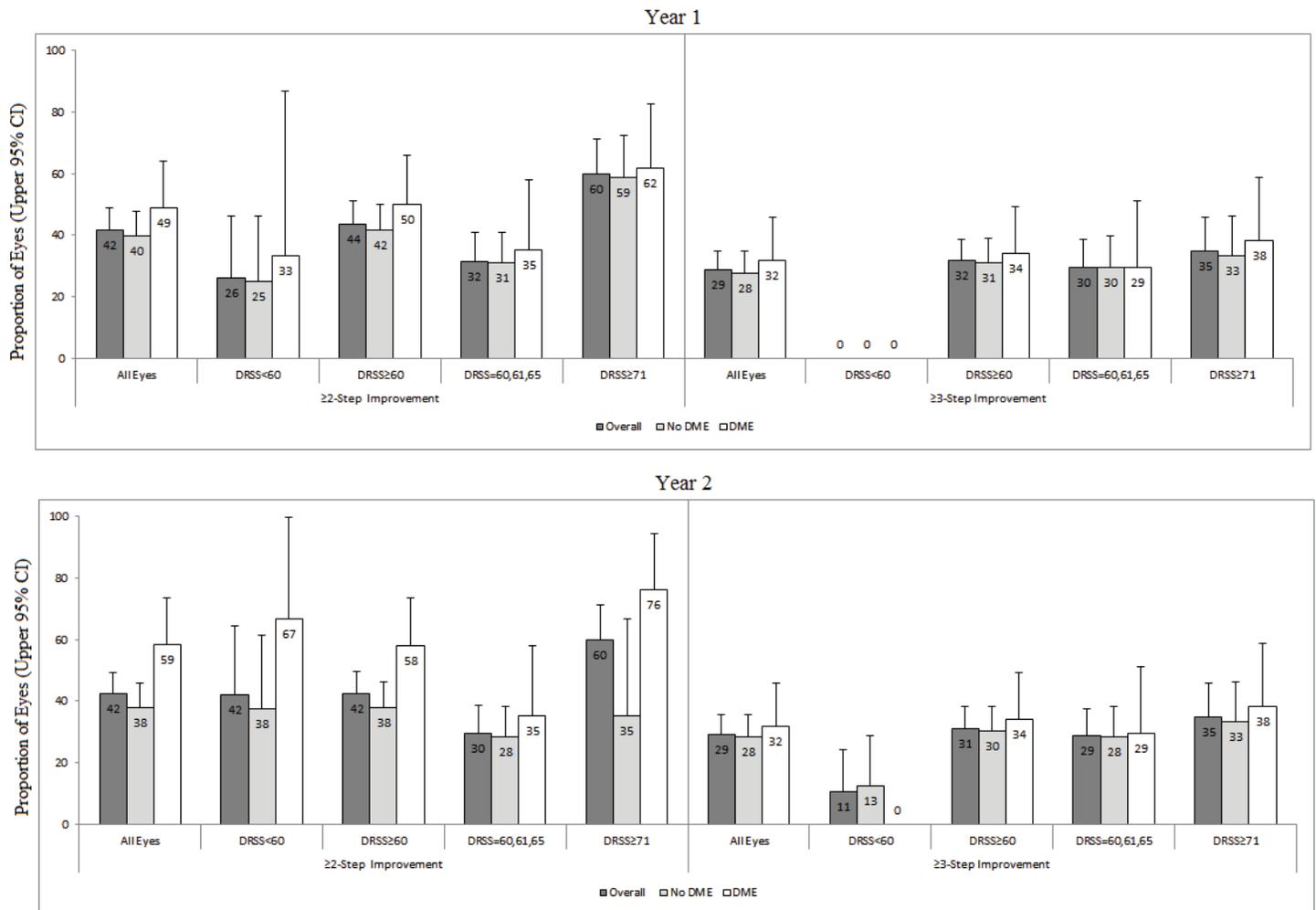
Visit	PRP with Ranibizumab			PRP without Ranibizumab
	Overall (N=110)	No DME (N=64)	DME (N=46)	No DME (N=93)
Baseline	72.4 (13.23)	78.0 (10.32)	64.7 (13.04)	78.5 (10.65)
Week 16	1.2 (9.40)	-0.6 (7.10)	3.7 (11.52)	-4.2 (14.97)
Week 32	2.3 (11.72)	0.3 (7.93)	5.2 (15.18)	-3.6 (16.62)
Week 52 (Year 1)	0.7 (14.77)	-1.9 (12.92)	4.2 (16.54)	-5.2 (22.71)
Week 68	-1.8 (17.88)	-4.0 (16.27)	1.4 (19.65)	-4.6 (21.21)
Week 84	0.7 (15.20)	-0.9 (11.55)	3.0 (19.08)	-3.8 (20.61)
Week 104 (Year 2)	-0.7 (17.61)	-2.1 (16.25)	1.2 (19.37)	-0.6 (12.53)

3.2.4.6 Efficacy Conclusion

A total of 394 eyes from 305 subjects were enrolled in Protocol S study; 191 eyes (42 eyes with DME and 149 eyes without DME) were randomized to the ranibizumab group and received ranibizumab 0.5 mg monthly for the first four injections and as needed afterwards: 10% of eyes enrolled in the study had severe NPDR or better (DRSS < 60) at baseline, 51% had mild-to-moderate PDR (DRSS=60, 61, 65), and 38% had high-risk PDR or worse (DRSS > 65).

Among all eyes in the ranibizumab group, about 42% (29%) of eyes showed ≥ 2 -step (≥ 3 -step) improvement at each time point (See Figure 6). The proportion of eyes with ≥ 3 -step improvement was comparable in eyes with or without DME; however, the proportion of eyes with ≥ 2 -step improvement was higher in eyes with DME by about 9% at year 1 and 20% at year 2 than in eyes without DME. When summarized by baseline DRSS, eyes with high-risk PDR or worse at baseline (DRSS ≥ 71) yielded greater improvement than what was seen in the overall population.

Figure 6: Proportion of Eyes in the Ranibizumab Group with ≥ 2 -Step and ≥ 3 -Step Improvement by DME Status (mITT Population, LOCF)



In summary, ranibizumab 0.5 mg injection administered monthly for the first four injections and as needed afterwards demonstrated substantial improvement in DR severity regardless of the DME status at baseline.

Even though ranibizumab 0.5 mg PRN demonstrated substantial benefit in improving DR severity regardless of DME, the applicant requested in this sBLA to expand ranibizumab 0.3 mg monthly dosing approved for the treatment of DR in patients with DME (based on RISE/RIDE studies) for a broad indication of treatment of DR regardless of DME. The applicant established a bridge between the ranibizumab 0.5 mg PRN dosing regimen used in Protocol S to the approved ranibizumab 0.3 mg monthly dosing regimen based on: (i) the consistency of results for ≥ 2 -step improvement across doses and regimens in Protocol S and in the RISE/RIDE studies, (ii) comparable averaged dose between 0.3 mg monthly over the first year and 0.5 mg PRN regimens that eyes without DME received over the first year, (iii) similar results from monthly 0.3 mg and monthly 0.5 mg in the RISE/RIDE studies, and (iv) similarity in disease pathology in DR patients with or without DME.

i) Consistency of Results in Protocol S and in the RISE/RIDE studies

In the RISE/RIDE studies, the treatment benefit of both ranibizumab 0.3 mg and 0.5 mg monthly dosing regimens were evaluated in the improvement of DR severity against sham treatment. In these studies, both dosing regimens demonstrated comparable benefit at year 2 and were superior to sham (see Table 21). The less frequent ranibizumab dosing regimen in Protocol S study also demonstrated substantial improvement in DRSS in eyes with DME; the high rate of improvement in Protocol S compared to in the RISE/RIDE studies is likely because Protocol S study enrolled a lot more eyes with high-risk PDR or worse at baseline (DRSS \geq Level 71) than in the RIDE/RIDE studies (See Table 5). When the analyses in Protocol S study was performed only in the subgroup of eyes with moderate PDR or better at baseline (that is similar to 94% of subjects enrolled in the RISE/RIDE studies), the improvement in DRSS in patients with DME was comparable across the studies.

Table 21: DRSS Improvement in Protocol S and in the Pooled RISE/RIDE Studies at Year 2

	RIDE/RISE Pooled ^[1]			Protocol S		Protocol S ^[2]	
	DME			DME	No DME	DME	No DME
	Sham (N=239)	0.3 mg (N=234)	0.5 mg (N=234)	0.5 mg PRN (N=41)	0.5 mg PRN (N=148)	0.5 mg PRN (N=20)	0.5 mg PRN (N=97)
≥ 2 -Step	5.4 (2.6, 8.3)	37.6 (31.4, 43.8)	35.9 (29.8, 42.0)	58.5 (43.5, 73.6)	37.8 (30.0, 45.7)	40.0 (18.5, 61.5)	29.9 (20.8, 39.0)
≥ 3 -Step	1.3 (0.0, 2.7)	13.2 (8.9, 17.6)	14.5 (10.0, 19.0)	31.7 (17.5, 46.0)	28.4 (21.1, 35.6)	25.0 (6.0, 44.0)	25.8 (17.1, 34.5)

Source: Table 7 of the RISE/RIDE studies statistical review; and Table 1 of Applicant Pre-sBLA post-meeting package

^[2] Includes eyes with moderate PDR or better at baseline

In Protocol S study, treatment with ranibizumab 0.5 mg PRN also demonstrated substantial improvement in eyes without DME. In this study, the proportion of eyes with ≥ 3 -Step improvement was comparable in eyes with or without DME although ≥ 2 -step improvement was slightly higher in eyes with DME.

In summary, in DR patients with DME, the improvement in DR severity at year 2 based on the treatment with ranibizumab 0.5 mg PRN in Protocol S study and the treatment with ranibizumab 0.3 mg monthly dosing in the RISE/RIDE studies was comparable. In Protocol S, the improvement in DR severity at year 2 based on treatment with ranibizumab 0.5 mg PRN was comparable in eyes with and

without DME. Therefore, even though there is no data to show the efficacy benefit of ranibizumab 0.3 mg monthly dosing in DR patients without DME, there is no reason to believe it behaves differently in these patients versus in patients with DME based on the consistency of the results.

ii) Treatment exposure with 0.3 mg monthly and 0.5 mg PRN regimens over the first year

The applicant indicated that the total amount of ranibizumab received during the first year was comparable between eyes without DME that received ranibizumab 0.5 mg PRN in Protocol S study and DR patients with DME that received ranibizumab 0.3 mg monthly dosing in the RISE/RIDE studies. In Protocol S study, eyes without DME received an average of 6.7 ranibizumab 0.5 mg injections during the first year for a total of about 3.4 mg ranibizumab (i.e., 6.7 injections X 0.5 mg). This is very similar to the total yearly amount of ranibizumab that DR patients with DME received in the RISE/RIDE studies (i.e., 12 X 0.3 mg = 3.6 mg).

In summary, the applicant justification for a bridge based on the consistency of results and comparable averaged dose between monthly 0.3 mg and 0.5 mg PRN appeared acceptable from the reviewer perspective. Regarding the similarity in disease pathology, we defer to the medical reviewer.

Therefore, based on the totality of evidence from the RIDE and RISE studies and the additional information in DR patients without DME provided in Protocol S study, the reviewer concludes that this application provides evidence of efficacy of ranibizumab 0.3 mg monthly dosing for a broad indication of treatment of DR regardless of DME status

3.3 Safety Evaluation

In Protocol S study, safety was assessed through exposure to study medication; and summary of ocular and non-ocular adverse events (AEs), serious AEs, and deaths. Safety was summarized according to the actual treatment received. Ocular AEs were summarized by safety evaluable eyes. Non-ocular AEs were summarized by safety evaluable subjects where summary for subjects with one study eye enrolled was provided by treatment group while for subjects with both eyes enrolled was provided without treatment group.

A high level safety summary up to Year 2 is summarized in this section; see the FDA medical review for a comprehensive safety evaluation.

i) Summary of Exposure to Treatment Medication

The summary of ranibizumab injections received prior to year 1 and year 2 is shown in [Table 22](#) by baseline DME status. All eyes in the ranibizumab group and a slight majority (54%) of eyes in the PRP group received at least one ranibizumab injection prior to year 2.

Table 22: Summary of Ranibizumab Injection Received Prior to Year 1 and Year 2

Group	N	Prior to Year 1					Prior to Year 2				
		n ^[1]	Sum	Mean (SD)	Median	Range	n ^[1]	Sum	Mean (SD)	Median	Range
PRP Group											
Overall	203	104	470	4.5 (3.29)	4.0	1 – 12	110	687	6.3 (5.15)	5.0	1 – 20
No DME	157	58	217	3.7 (2.93)	3.0	1 – 12	64	310	4.8 (4.00)	4.0	1 – 18
DME	46	46	253	5.5 (3.49)	5.0	1 – 12	46	377	8.2 (5.93)	7.0	1 – 20
Ranibizumab Group											
Overall	191	191	1354	7.1 (2.46)	7.0	2 – 13	191	1983	10.4 (4.93)	10.0	2 – 22
No DME	149	149	995	6.7 (2.31)	6.0	2 – 13	149	1461	9.8 (4.72)	9.0	2 – 21
DME	42	42	359	8.6 (2.47)	9.0	5 – 13	42	522	12.4 (5.15)	12.5	5 – 22

Source: Applicant Summary of Clinical Safety Table 1

^[1]Number of eyes that received ranibizumab injection

The summary of the initial and supplemental PRP treatment received prior to year 2 is shown in [Table 23](#) by baseline DME status. All eyes in the PRP group and a total of 13 eyes in the ranibizumab group received PRP treatment prior to year 2. About 45% of eyes in the PRP group and only one eye in the ranibizumab group received supplemental PRP treatment prior to year 2.

Table 23: Summary of PRP Treatment Received Prior to Year 2

Treatment	Group	N	Initial PRP	Supplemental PRP
PRP	Overall	203	203 (100%)	92 (45.3%)
	No DME	157	157 (100%)	77 (49.0%)
	DME	46	46 (100%)	15 (32.6%)
Ranibizumab	Overall	191	13 (6.8%)	1 (0.5%)
	No DME	149	7 (4.7%)	0
	DME	42	6 (2.4%)	1 (2.4%)

Source: Applicant Summary of Clinical Safety Table 1

ii) Summary of Ocular Adverse Event

In Protocol S study, the frequency of ocular AEs in the ranibizumab and PRP group was, respectively, 86% and 85% in eyes with DME and 78% and 80% in eyes without DME. The most

frequent ocular AEs reported in the ranibizumab group were: *vitreous floaters* (31%), *vitreous haemorrhage* (20%), and *blurred vision* (15%) in the subgroup of eyes without DME; and *vitreous haemorrhage* (24%), *blurred vision* (21%), *vitreous floaters* (19%), and *reduced visual acuity* (19%) in the subgroup of eyes with DME.

A total of five eyes experienced at least one serious ocular adverse event (SAE): (i) three eyes in the ranibizumab group (one eye with DME experienced *vitreous haemorrhage*; and 2 eyes without DME with one eye experienced *sudden visual loss, visual impairment, and vitreous floaters* and the other eye experienced *endophthalmitis*) and (ii) two eyes in the PRP group with DME at baseline both experienced *vitreous haemorrhage*.

No patient discontinued from the study drug prematurely due to an ocular AE or SAE during the 2 years treatment period.

iii) Summary of Non-Ocular Adverse Event

The high-level non-ocular AE summary is shown in Table below. More subjects in the ranibizumab group experienced at least one non-ocular AE during the study compared to in the PRP group. Within each group the rate of non-ocular AE was comparable in subjects with and without DME.

	One Study Eye				Two Study Eye	
	Ranibizumab		PRP		Ranibizumab/PRP	
	DME (N=21)	No DME (N=81)	DME (N=25)	No DME (N=89)	DME (N=29)	No DME (N=60)
Total number of subjects with at least one AE	19 (90.5%)	73 (90.1%)	20 (80.0%)	71 (79.8%)	26 (89.7%)	55 (91.7%)
Total number of subjects with at least one SAE	13 (61.9%)	36 (44.4%)	9 (36.0%)	33 (37.1%)	10 (34.5%)	28 (46.7%)
Any Sever SAE	10 (47.6%)	33 (40.7%)	9 (36.0%)	27 (30.3%)	8 (27.6%)	22 (36.7%)
Discontinuation from treatment due to AE/SAE	2 (9.5%)	4 (4.9%)	0	2 (2.2%)	1 (3.4%)	3 (5.0%)

Source: Table 5 of Applicant Summary of Clinical Safety

A total of 14 subjects died during the 2 years treatment period: 10 subjects with a single eye enrolled (4 in the PRP group and 6 in the ranibizumab group) and 4 subjects with both eyes enrolled. The summary of the number of death by treatment group and baseline DME status is shown in [Table 24](#). The results from the pooled RISE/RIDE studies are also presented for comparison purpose.

Table 24: Summary of Number of Deaths Reported by Treatment Group and Baseline DME Status

	Protocol S Study			RISE/RIDE Pooled ^[1]	
	One Study Eye		Two Study Eye	Ranibizumab	
	PRP	Ranibizumab 0.5 mg PRN	PRP/Ranibizumab	0.3 mg	0.5 mg
DME 95% CI	8.0% (2/25) (0.1%, 26.0%)	14.3% (3/21) (3.0%, 36.0%)	3.4% (1/29) (0.1%, 17.8%)	2.8% (7/250) (1.1%, 5.7%)	4.4% (11/250) (2.2%, 7.7%)
No DME 95% CI	2.2% (2/89) (0.3%, 7.9%)	3.7% (3/81) (0.8%, 10.4%)	5.0% (3/60) (1.0%, 13.9%)	--	--
Overall 95% CI	3.5% (4/114) (1.0%, 8.7%)	5.9% (6/102) (2.2%, 12.4%)	4.5% (4/89) (1.2%, 11.1%)	2.8% (7/250) (1.1%, 5.7%)	4.4% (11/250) (1.1%, 5.7%)

^[1] Source: Table 20 of statistical review for the RISE/RIDE studies; Confidence Intervals (CI) were calculated by the reviewer.

In Protocol S study, the death rate in the ranibizumab group was slightly higher than in the PRP group; and the rate was higher in subjects with DME than without DME. When compared to in the RISE/RIDE studies, the death rate in ranibizumab 0.5 mg PRN in Protocol S was almost twice that of ranibizumab 0.3 mg monthly dosing in the RISE/RIDE studies.

The applicant also summarized the rate of Antiplatelet Trialists' Collaboration (APTC) events experienced during the 2 years treatment period. The APTC events included: *all non-fatal myocardial infarction (MI), non-fatal cerebral vascular accident (CVA), vascular deaths, and deaths of unknown cause*. The summary of the APTC events in Protocol S study during the 2 years treatment period are shown in Table 25 by treatment group and baseline DME status. The results from the pooled RISE/RIDE studies are also presented in the table for comparison purpose.

In Protocol S study, the rate of APTC events was slightly higher in ranibizumab group than in the PRP group; and the rate was much higher in eyes with DME than without DME. When compared to in the RISE/RIDE studies, treatment with ranibizumab 0.3 mg monthly dosing had a lower APTC rate than treatment with ranibizumab 0.5 mg PRN.

Table 25: Summary of APTC Events Reported During the Study

	Protocol S Study [1]						Pooled RISE/RIDE Studies [2]	
	Subjects with One Study Eye				Subjects with Two Study Eyes		Ranibizumab	
	Ranibizumab 0.5 mg PRN		PRP		Ranibizumab/PRP		0.3 mg	0.5 mg
	DME (N=21)	No DME (N=81)	DME (N=25)	No DME (N=89)	DME (N=29)	No DME (N=60)	DME (N=250)	DME (N=250)
Any Event	5 (23.8%)	7 (8.6%)	4 (16.0%)	8 (9.0%)	1 (3.4%)	6 (10.0%)	16 (6.4%)	22 (8.8%)
Death: Overall	3 (14.3%)	3 (3.7%)	2 (8.0%)	2 (2.2%)	1 (3.4%)	3 (5.0%)	7 (2.8%)	11 (4.4%)
Vascular	0	1 (1.2%)	0	1 (1.1%)	1 (3.4%)	1 (1.7%)	5 (2.0%)	6 (2.4%)
Non-vascular	1 (4.8%)	1 (1.2%)	2 (8.0%)	1 (1.1%)	0	1 (1.7%)	2 (0.8%)	4 (1.6%)
Unknown Cause	2 (9.5%)	1 (1.2%)	0	0	0	1 (1.7%)	0	1 (0.4%)
MI or CVA: Overall	2 (9.5%)	4 (4.9%)	2 (8.0%)	6 (6.7%)	1 (3.4%)	4 (6.7%)	12 (4.8%)	14 (5.6%)
MI: Overall	2 (9.5%)	1 (1.2%)	0	4 (4.5%)	0	3 (5.0%)	9 (3.6%)	7 (2.8%)
Fatal	0	0	0	0	0	1 (1.7%)	2 (0.8%)	1 (0.4%)
Non-Fatal	2 (9.5%)	1 (1.2%)	0	4 (4.5%)	0	2 (3.3%)	7 (2.8%)	6 (2.4%)
CVA: Overall	0	3 (3.7%)	2 (8.0%)	2 (2.2%)	1 (3.4%)	1 (1.7%)	3 (1.2%)	8 (3.2%)
Fatal	0	0	0	0	1 (3.4%)	0	1 (0.4%)	3 (1.2%)
Non-Fatal	0	3 (3.7%)	2 (8.0%)	2 (2.2%)	0	1 (1.7%)	2 (0.8%)	5 (2.0%)
APTC Events	4 (19.0%)	6 (7.4%)	2 (8.0%)	7 (7.9%)	1 (3.4%)	5 (8.3%)	14 (5.6%)	18 (7.2%)
Exact 95% CI	(5.4%, 41.9%)	(2.8%, 15.4%)	(1.0%, 26.0%)	(3.2%, 15.5%)	(0.1%, 17.8%)	(2.8%, 18.4%)	(3.1%, 9.2%)	(4.3%, 11.1%)

1] Source: Applicant Summary of Clinical Safety Table; [2] Source: Table 19 of statistical review for the RISE/RIDE studies

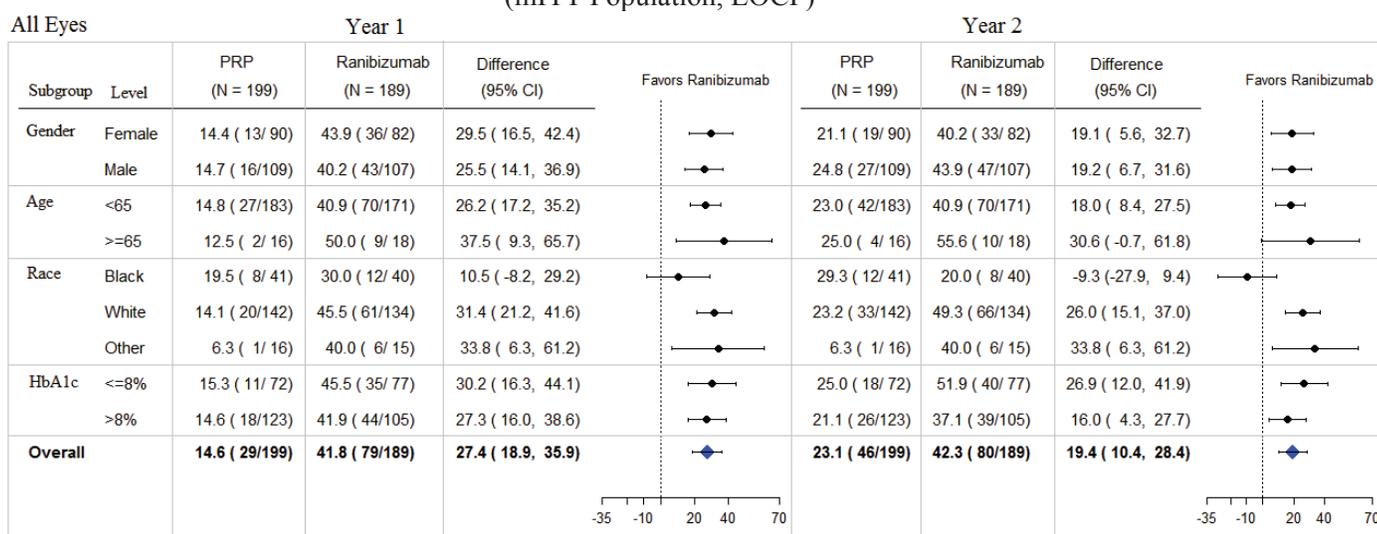
In summary, the eyes in the ranibizumab group in Protocol S study experienced a slightly higher rate of ocular and non-ocular AEs compared to the eyes in the PRP group during the 2 years treatment period. Furthermore, the death rate and the rate of APTC events during the 2 years treatment period was higher in the ranibizumab group (regardless of the DME status) than in the PRP group in Protocol S study and in the ranibizumab 0.3 mg monthly dosing in the pooled RISE/RIDE studies.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The proportion of eyes with ≥ 2 -step and ≥ 3 -step improvement in DRSS at year 1 and year 2 are summarized for the subgroups of gender, age, race, and HbA1c category. Summaries were presented for all eyes and for eyes without DME. For each case, the proportions of eyes with DRSS improvement and the treatment differences in proportions are shown in Figure 7 and Figure 8. Due to the small number of eyes with DME at baseline enrolled in the study, subgroup analysis was not performed for this subgroup of eyes.

In all eyes and in eyes without DME at baseline, the results in each of the subgroups levels were consistent with the overall population. In some subgroups there were only small number of eyes and the results for these subgroups may not be indicative of the overall treatment effects.

Figure 7: Proportion of Eyes with ≥ 2 -Step Improvement by Subgroup (mITT Population, LOCF)



Eyes without DME at baseline

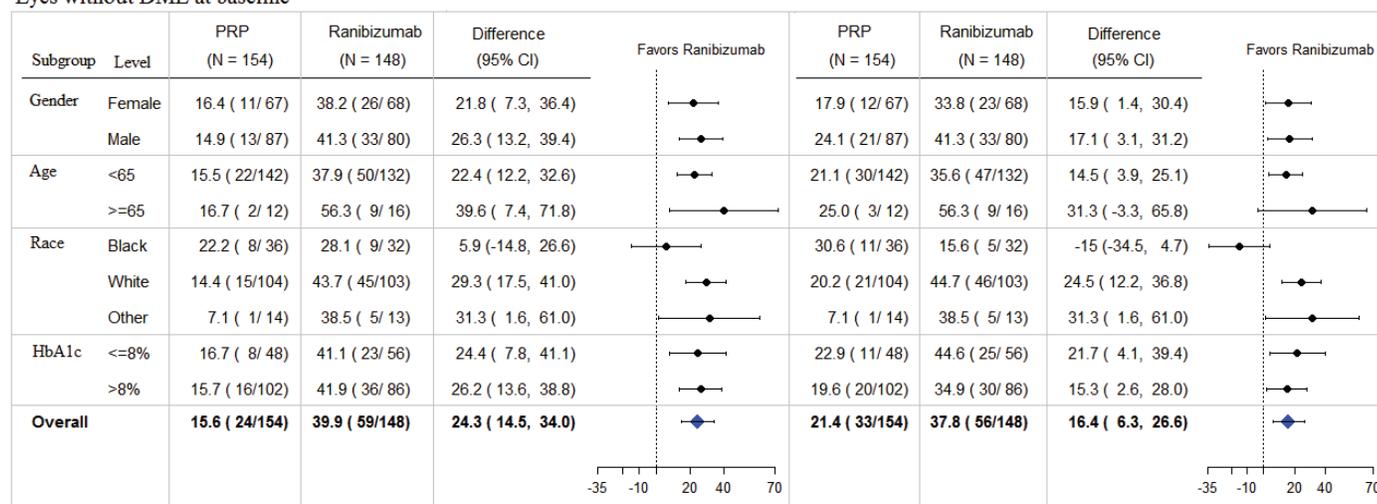
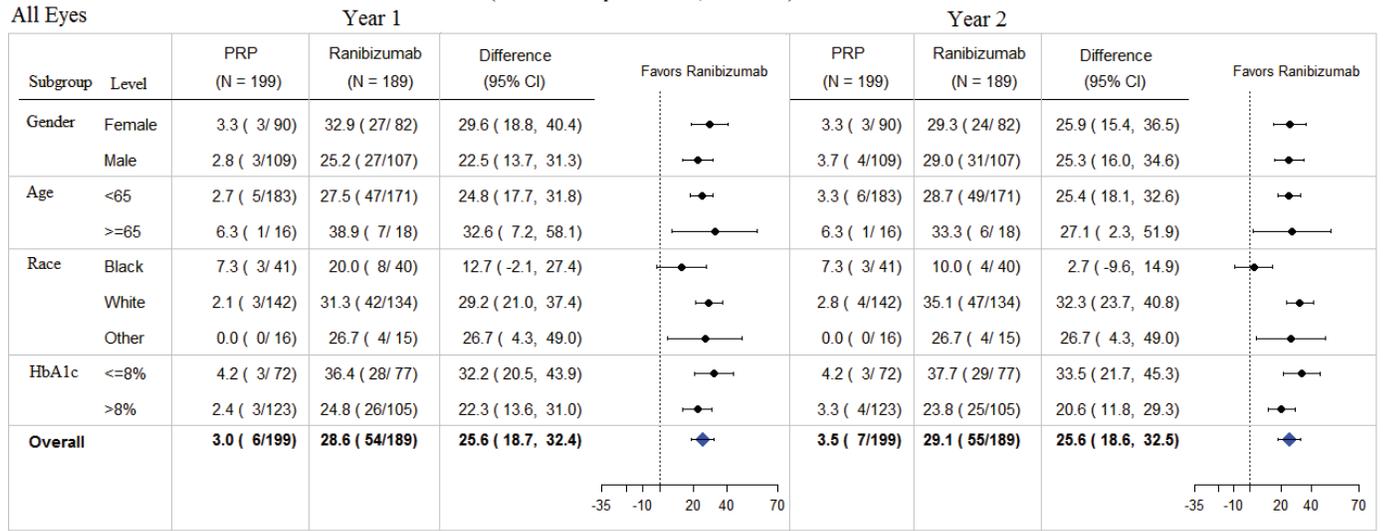
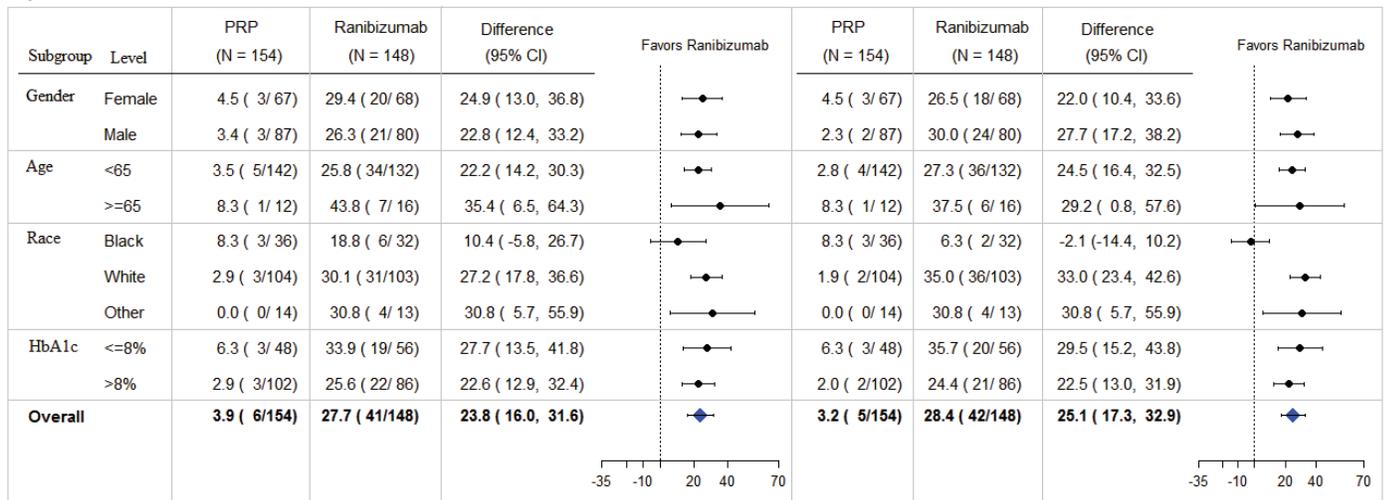


Figure 8: Proportion of Eyes with ≥ 3 -Step Improvement by Subgroup (mITT Population, LOCF)



Eyes without DME at Baseline



The pattern in Black/African American race appeared slightly different from the overall population, mainly for ≥ 2 -Step improvement (See Figure 7). In this subgroup, PRP-treated eyes appeared to show numerically better improvement than ranibizumab treated-eyes at year 2 but the result in this subgroup was highly confounded by the ranibizumab injection received during the study (See Table below).

Proportion of eyes with ≥ 2 -Step Improvement at Year 2 in PRP-treated eyes with or without ranibizumab (in Black/African American)

	PRP			Ranibizumab
	Without Ranibizumab	With Ranibizumab	Overall	
All Eyes	15.0 (3/ 20)	42.9 (9/ 21)	29.3 (12/41)	20.0 (8/ 40)
Eyes without DME	15.0 (3/ 20)	50.0 (8/ 16)	30.6 (11/36)	15.6 (5/32)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified in this review. The reviewer has addressed the following issues that were raised during the pre-BLA meetings and/or in the sBLA review:

- i) The sBLA was based on a single Phase 3 study, and efficacy endpoints to support the sBLA were defined post-hoc. Even though endpoints were defined post-hoc, the treatment effects seen in the study were substantial in light of the progressively worsening nature of the disease and in comparison to the very low placebo (sham) rates in the RIDE/RISE studies. Furthermore, the treatment effect in the study is consistent with the results in the RIDE/RISE studies that were used for the approval of ranibizumab 0.3 mg monthly injection for the treatment of DR in patients with DME.
- ii) Although ranibizumab 0.5 mg PRN was determined effective in improving DR severity in DR patients regardless of DME, the applicant requested to broaden the indication to treatment of DR regardless of DME for the approved dose of ranibizumab 0.3 mg monthly. The applicant established a bridge between ranibizumab 0.5 mg PRN dosing regimen used in Protocol S to the current approved ranibizumab 0.3 mg monthly dosing based on the following considerations: (i) the consistency of results for ≥ 2 -step improvement across doses and regimens in Protocol S and in the RISE/RIDE studies, (ii) comparable averaged amounts of ranibizumab between 0.3 mg monthly and 0.5 mg PRN regimens over the first year for eyes without DME, (iii) similar results for monthly 0.3 mg and 0.5 mg in the RISE/RIDE studies, and (iii) similarity in disease pathology in DR patients with or without DME. The applicant's justification for a bridge based on the consistency of results and comparable averaged dose between monthly 0.3 mg and 0.5 mg PRN appeared acceptable from the reviewer perspective.
- iii) A head-to-head treatment comparison between the ranibizumab and PRP group based on all eyes would not be meaningfully interpreted in the study because the majority of PRP-treated eyes could not achieve the improvement criteria due to the nature of the DRSS grading scheme involved with the PRP-induced scars. Despite this limitation, in the subgroup of eyes where both treatment groups could achieve improvement, ranibizumab treatment still provided numerically better improvement than PRP.
- iv) For the 305 subjects enrolled in the study, a single eye was enrolled for 216 subjects and both eyes were enrolled for 89 subjects. For subjects with both eyes enrolled, one eye received ranibizumab and the other eye received PRP randomly. Although eyes within each treatment group were from independent subjects, analyses of treatment comparison should take the correlation from subjects with two study eyes into account. The correlation in the change in DRSS in eyes from the 89 subjects with both eyes enrolled was weak in the study but positive. Therefore, the impact on the overall conclusion of treatment comparisons that ignored the correlation was minimal. To assess the impact of ignoring the correlation, the reviewer conducted treatment comparison based on bootstrap re-sampling approach that takes the correlation into account. The overall conclusion was unchanged.

5.2 Collective Evidence

Ranibizumab 0.5 mg injection administered monthly for the first four injections and as needed afterwards demonstrated significant improvement in DR severity in patients with DR regardless of DME. About 42% of eyes (95% CI: 35% to 49%) and 29% of eyes (95% CI: 23% to 36%) in the ranibizumab group demonstrated ≥ 2 -step and ≥ 3 -step improvement at Year 2, respectively. In this treatment group, eyes with DME at baseline showed numerically better improvement than those without DME at Year 2 (59% versus 39% for ≥ 2 -step improvement and 32% versus 28% for ≥ 3 -step improvement). The difference in the rate of improvement may be likely because the DME group enrolled more eyes with high-risk PDR or worse at baseline (50% versus 34%) and received more injections on average prior to 2 years (12.4 versus 9.8) than the non-DME group.

When summarized by baseline DRSS, the eyes in the ranibizumab group with high-risk PDR or worse at baseline (DRSS $>$ 65) demonstrated substantial improvement at Year 2; for example, about 60% (95% CI: 48% to 71%) and 35% (95% CI: 24% to 46%) of eyes in this subgroup showed ≥ 2 -step and ≥ 3 -step improvement, respectively.

Very few eyes in the ranibizumab group had worsening in DRSS from baseline at Year 2; for example, $<$ 4% and about 2% of eyes had ≥ 2 -step and ≥ 3 -step worsening.

The treatment benefit with ranibizumab was also seen in 54% of eyes in the PRP group that also received ranibizumab injection during the study.

Overall, the DRSS improvements with the ranibizumab treatment were substantial in light of the progressively worsening nature of the disease and in comparison to the very low placebo (sham) rates (5% for ≥ 2 -step improvement and 1% for ≥ 3 -step improvement) in the RIDE/RISE studies.

In terms of safety evaluation, eyes in the ranibizumab group in Protocol S study experienced a slightly higher rate of ocular and non-ocular AEs compared to eyes in the PRP group.

Furthermore, the death rate and the rate of APTC events during the 2 years was higher in the ranibizumab group (regardless of the DME status) than in the PRP group in Protocol S study and in ranibizumab 0.3 mg monthly dosing in the pooled RISE/RIDE studies.

5.3 Conclusion and Recommendation

The reviewer concludes that this application provides evidence of efficacy of ranibizumab 0.3 mg monthly dosing for a broad indication of treatment of DR regardless of DME status.

The conclusion is based on the totality of evidence from the RIDE/RISE studies and the additional information in DR patients with and without DME provided in the Protocol S study, and the well-established safety profile of monthly ranibizumab 0.3 mg dosing and knowledge that the same dosing regimen is already approved for the treatment of DR in patients with DME

5.4 Labeling Recommendation

In the clinical study section of the label (Section (b) (4) Diabetic Retinopathy), the applicant proposed to include the efficacy results of the proportion of eyes with ≥ 3 -step improvement at year 2 (by DME status) for the ranibizumab group only. Although the reviewer has no objection including the results for the ranibizumab group only from Protocol S study (D-3), we have the following edits and recommendations for the label:

Applicant's Proposal (Reviewer's edit/recommendation are in blue color):

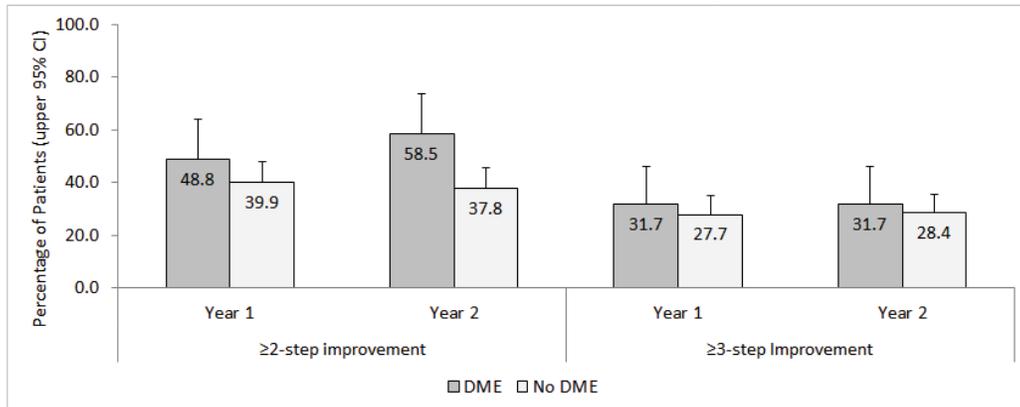
Study D-3 enrolled DR patients with and without DME; 88 (22%) eyes with baseline DME and 306 (78%) eyes without baseline DME and balanced across treatment groups. Study D-3 was a randomized, active-controlled study where patient age ranged from 20 to 83 with a mean age of 51 years. A total of 394 study eyes from 305 patients, including 89 who had both eyes randomized, were enrolled (LUCENTIS, 191 study eyes; pan-retinal photocoagulation; 203 study eyes). All eyes in the LUCENTIS group received a baseline 0.5 mg intravitreal injection followed by 3 monthly intravitreal injections, after which treatment was guided by pre-specified re-treatment criteria. Patients had baseline ETDRS-DRSS ranging from 20 to 85. At baseline, 11% of eyes had NPDR (ETDRS-DRSS < 60), 50% had mild-to-moderate PDR (ETDRS-DRSS = 60, 61, or 65), and 37% had high-risk PDR (b) (4) (ETDRS-DRSS ≥ 71).

An analysis of data from Study D-3 demonstrated that at Year 2 in the LUCENTIS group, 31.7% and 28.4% of eyes in the subgroups with baseline DME and without baseline DME, respectively, had ≥ 3 -step improvement from baseline in ETDRS-DRSS.

Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement from Baseline in ETDRS-DRSS at Year 2 in Study D-3

Outcome Measure (in ETDRS-DRSS)	LUCENTIS group	
	Eyes with Baseline DME n = 41	Eyes without Baseline DME n = 148
≥ 3 step improvement from baseline 95% CI for percentage	13 (31.7%) (17.5%, 46.0%)	42 (28.4%) (21.1%, 35.6%)
≥ 2 step improvement from baseline 95% CI for percentage	24 (58.5%) (43.5%, 73.60%)	56 (37.8%) (30.0%, 45.7%)

Mock Figure: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement from Baseline in ETDRS-DRSS at Year 1 and Year 2 in Study D-3



APPENDIX:

Table 26: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement: PRP Group without Ranibizumab Injection versus Ranibizumab Group (mITT Population, LOCF)

≥ 2 -step improvement

Visit	Baseline Value	PRP without Ranibizumab	Ranibizumab	Difference (95% CI)
Year 1	Overall	8.9 (8/ 90)	41.8 (79/189)	31.6 (21.7, 41.5)
	Moderate PDR or Better (\leq Level 65)	1.6 (1/ 62)	30.8 (36/117)	29.4 (19.2, 39.7)
	High-risk PDR or worse (\geq Level 71)	25.0 (7/ 28)	59.7 (43/ 72)	33.3 (12.2, 54.5)
	High-risk PDR (71A - 71D)	26.3 (5/ 19)	59.6 (28/ 47)	35.1 (9.2, 61.1)
	High-risk PDR or worse (\geq Level 75)	22.2 (2/ 9)	60.0 (15/ 25)	30.3 (-6.0, 66.5)
Year 2	Overall	17.8 (16/ 90)	42.3 (80/189)	20.8 (9.6, 32.0)
	Moderate PDR or Better (\leq Level 65)	1.6 (1/ 62)	31.6 (37/117)	31.0 (20.7, 41.2)
	High-risk PDR or worse (\geq Level 71)	53.6 (15/ 28)	59.7 (43/ 72)	-0.3 (-23.5, 22.8)
	High-risk PDR (71A - 71D)	68.4 (13/ 19)	61.7 (29/ 47)	-10 (-36.9, 16.9)
	High-risk PDR or worse (\geq Level 75)	22.2 (2/ 9)	56.0 (14/ 25)	21.1 (-13.9, 56.0)

≥ 3 -step improvement

Visit	Baseline Value	PRP without Ranibizumab	Ranibizumab	Difference (95% CI)
Year 1	Overall	2.2 (2/ 90)	28.6 (54/189)	25.7 (17.8, 33.7)
	Moderate PDR or Better (\leq Level 65)	1.6 (1/ 62)	24.8 (29/117)	23.5 (13.8, 33.2)
	High-risk PDR or worse (\geq Level 71)	3.6 (1/ 28)	34.7 (25/ 72)	29.5 (14.5, 44.5)
	High-risk PDR (71A - 71D)	0.0 (0/ 19)	31.9 (15/ 47)	35.8 (19.4, 52.2)
	High-risk PDR or worse (\geq Level 75)	11.1 (1/ 9)	40.0 (10/ 25)	17.1 (-12.3, 46.5)
Year 2	Overall	2.2 (2/ 90)	29.1 (55/189)	26.8 (18.8, 34.8)
	Moderate PDR or Better (\leq Level 65)	1.6 (1/ 62)	25.6 (30/117)	26.3 (16.3, 36.3)
	High-risk PDR or worse (\geq Level 71)	3.6 (1/ 28)	34.7 (25/ 72)	30.1 (15.1, 45.1)
	High-risk PDR (71A - 71D)	0.0 (0/ 19)	34.0 (16/ 47)	38.4 (21.8, 55.0)
	High-risk PDR or worse (\geq Level 75)	11.1 (1/ 9)	36.0 (9/ 25)	13.2 (-15.3, 41.6)

Table 27: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement (Sensitivity Analysis)
(mITT Population)

Visit	≥ 2 -step Improvement Baseline DRSS	Un-adjusted		Adjusted		Difference (95% CI)
		PRP	Ranibizumab	PRP	Ranibizumab	
Year 1	Overall	14.6 (29/199)	41.8 (79/189)	14.7 (9.8, 19.6)	42.0 (35.1, 49.0)	27.4 (18.9, 35.9)
	Moderate PDR or Better (≤ 65)	1.6 (2/125)	30.8 (36/117)	1.7 (-0.6, 4.0)	31.7 (23.3, 40.2)	30.0 (21.2, 38.9)
	High-risk PDR or worse (>65)	36.5 (27/74)	59.7 (43/72)	36.8 (26.1, 47.5)	59.5 (48.1, 71.0)	22.7 (7.1, 38.4)
	High-risk PDR (71A - 71D)	35.8 (19/53)	59.6 (28/47)	35.9 (23.1, 48.8)	59.5 (45.3, 73.8)	23.6 (4.5, 42.8)
	High-risk PDR or worse (>71)	38.1 (8/21)	60.0 (15/25)	36.4 (19.1, 53.8)	58.1 (38.7, 77.5)	21.7 (-4.4, 47.7)
Year 2	Overall	20.6 (41/199)	35.4 (67/189)	20.7 (15.1, 26.2)	35.6 (28.9, 42.4)	15.0 (6.2, 23.7)
	Moderate PDR or Better (≤ 65)	0.8 (1/125)	28.2 (33/117)	1.0 (-0.9, 2.8)	29.7 (21.4, 37.9)	28.7 (20.2, 37.1)
	High-risk PDR or worse (>65)	54.1 (40/74)	47.2 (34/72)	55.1 (43.8, 66.4)	48.1 (36.8, 59.4)	-7.0 (-23.0, 8.9)
	High-risk PDR (71A - 71D)	58.5 (31/53)	51.1 (24/47)	58.5 (45.1, 72.0)	51.9 (37.8, 66.0)	-6.6 (-26.1, 12.8)
	High-risk PDR or worse (>71)	42.9 (9/21)	40.0 (10/25)	44.2 (24.0, 64.4)	38.2 (21.0, 55.4)	-6.0 (-32.5, 20.5)

Visit	≥ 3 -step Improvement Baseline DRSS	Un-adjusted		Adjusted		Difference (95% CI)
		PRP	Ranibizumab	PRP	Ranibizumab	
Year 1	Overall	3.0 (6/199)	28.6 (54/189)	3.0 (0.7, 5.3)	28.7 (22.3, 35.1)	25.7 (18.9, 32.6)
	Moderate PDR or Better (≤ 65)	0.8 (1/125)	24.8 (29/117)	1.0 (-0.9, 2.8)	25.3 (17.3, 33.3)	24.3 (16.2, 32.5)
	High-risk PDR or worse (>65)	6.8 (5/74)	34.7 (25/72)	7.7 (1.6, 13.8)	34.5 (23.5, 45.6)	26.8 (14.2, 39.5)
	High-risk PDR (71A - 71D)	0.0 (0/53)	31.9 (15/47)	0.0 (0.0, 0.0)	32.1 (18.7, 45.6)	32.1 (18.7, 45.6)
	High-risk PDR or worse (>71)	23.8 (5/21)	40.0 (10/25)	23.8 (11.0, 36.5)	37.1 (19.0, 55.2)	13.4 (-8.8, 35.5)
Year 2	Overall	3.5 (7/199)	25.4 (48/189)	3.5 (1.0, 6.0)	25.5 (19.3, 31.7)	22.0 (15.3, 28.7)
	Moderate PDR or Better (≤ 65)	0.8 (1/125)	23.1 (27/117)	1.0 (-0.9, 2.8)	24.2 (16.4, 31.9)	23.2 (15.2, 31.2)
	High-risk PDR or worse (>65)	8.1 (6/74)	29.2 (21/72)	9.1 (2.3, 15.9)	29.9 (19.3, 40.5)	20.8 (8.2, 33.4)
	High-risk PDR (71A - 71D)	0.0 (0/53)	31.9 (15/47)	0.0 (0.0, 0.0)	32.0 (18.8, 45.3)	32.0 (18.8, 45.3)
	High-risk PDR or worse (>71)	28.6 (6/21)	24.0 (6/25)	31.0 (13.3, 48.6)	21.5 (8.0, 35.0)	-9.5 (-31.7, 12.7)

Note: Eyes with missing DRSS data were treated as non-responders.

Table 28: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement (Multiple Imputation) (mITT Population)

≥ 2-step Improvement	Year 1			Year 2		
	PRP (95% CI)	Ranibizumab (95% CI)	Difference (95% CI)	PRP (95% CI)	Ranibizumab (95% CI)	Difference (95% CI)
Overall	15.5 (10.4, 20.7)	42.5 (35.4, 49.5)	26.9 (18.2, 35.7)	21.5 (15.7, 27.4)	36.6 (29.7, 43.6)	15.1 (6.1, 24.1)
Moderate PDR or Better (≤ 65)	2.2 (-0.6, 5.0)	32.2 (23.6, 40.7)	30.0 (20.9, 39.0)	1.9 (-1.1, 4.8)	30.6 (22.1, 39.2)	28.8 (19.7, 37.8)
High-risk PDR or worse (>65)	38.3 (27.2, 49.3)	60.0 (48.4, 71.5)	21.7 (5.8, 37.7)	55.9 (44.5, 67.4)	49.0 (37.3, 60.8)	-6.9 (-23.2, 9.4)
High-risk PDR (71A - 71D)	36.8 (23.7, 50.0)	59.8 (45.5, 74.0)	22.9 (3.5, 42.4)	59.0 (45.3, 72.8)	52.4 (38.1, 66.7)	-6.7 (-26.4, 13.0)
High-risk PDR or worse (>71)	39.0 (20.6, 57.4)	58.7 (38.9, 78.5)	19.7 (-7.4, 46.7)	45.4 (24.5, 66.4)	39.1 (20.8, 57.5)	-6.3 (-33.6, 20.9)

Note: The Placebo (sham) rate for the proportion of subjects with ≥ 2 -step improvement in the pooled RISE/RIDE studies were used to impute missing binary data: success rate of 2.5% at year 1 and 5.4% at year 2 were used to impute missing data at the respective visits; 20 datasets were generated and the results from each dataset were combined using PROC MIANALYZE.

≥ 3-step Improvement	Year 1			Year 2		
	PRP (95% CI)	Ranibizumab (95% CI)	Difference (95% CI)	PRP (95% CI)	Ranibizumab (95% CI)	Difference (95% CI)
Overall	3.5 (0.8, 6.3)	28.9 (22.4, 35.4)	25.4 (18.3, 32.4)	3.6 (1.0, 6.2)	25.8 (19.5, 32.0)	22.2 (15.4, 29.0)
Moderate PDR or Better (≤ 65)	1.2 (-1.0, 3.3)	25.5 (17.5, 33.5)	24.3 (16.0, 32.6)	1.1 (-1.0, 3.2)	24.4 (16.5, 32.3)	23.3 (15.2, 31.5)
High-risk PDR or worse (>65)	8.8 (2.0, 15.6)	34.8 (23.6, 46.0)	25.9 (12.8, 39.1)	9.1 (2.3, 16.0)	30.2 (19.5, 40.9)	21.1 (8.4, 33.7)
High-risk PDR (71A - 71D)	0.6 (-2.6, 3.8)	32.3 (18.8, 45.8)	31.7 (17.8, 45.6)	0.0 (0.0, 0.0)	32.3 (19.0, 45.7)	32.3 (19.0, 45.7)
High-risk PDR or worse (>71)	26.0 (11.7, 40.4)	37.1 (18.6, 55.6)	11.1 (-12.5, 34.7)	31.1 (13.2, 48.9)	21.3 (7.2, 35.5)	-9.7 (-32.2, 12.7)

Note: Placebo (sham) rate for the proportion of subjects with ≥ 3 -step improvement in the pooled RISE/RIDE studies were used to impute missing binary data: success rate of 1.3% was used to impute missing data at both visits; 20 datasets were generated and the results from each dataset were combined using PROC MIANALYZE.

Table 29: Proportion of Eyes with ≥ 2 -Step and ≥ 3 -Step Improvement: Ranibizumab Group with DME versus without DME at Baseline (mITT Population; LOCF)

Visit	Baseline Value	≥ 2 -Step Improvement			≥ 3 -Step Improvement		
		No DME % (n/N) 95% CI	DME % (n/N) 95% CI	Difference (95% CI)	No DME % (n/N) 95% CI	DME % (n/N) 95% CI	Difference (95% CI)
Week 52	Overall	39.9 (59/148) (32.0, 47.8)	48.8 (20/41) (33.5, 64.1)	8.9 (-8.3, 26.1)	27.7 (41/148) (20.5, 34.9)	31.7 (13/41) (17.5, 46.0)	4.0 (-12.0, 20.0)
	Moderate PDR or Better (\leq Level 65)	29.9 (29/97) (20.8, 39.0)	35.0 (7/20) (14.1, 55.9)	5.1 (-17.7, 27.9)	24.7 (24/97) (16.2, 33.3)	25.0 (5/20) (6.0, 44.0)	0.3 (-20.6, 21.1)
	High-risk PDR or worse (\geq Level 71)	58.8 (30/51) (45.3, 72.3)	61.9 (13/21) (41.1, 82.7)	3.1 (-21.7, 27.9)	33.3 (17/51) (20.4, 46.3)	38.1 (8/21) (17.3, 58.9)	4.8 (-19.7, 29.2)
	High-risk PDR (71A - 71D)	61.8 (21/34) (45.4, 78.1)	53.8 (7/13) (26.7, 80.9)	-7.9 (-39.6, 23.7)	35.3 (12/34) (19.2, 51.4)	23.1 (3/13) (0.2, 46.0)	-12 (-40.2, 15.8)
	High-risk PDR or worse (\geq Level 75)	52.9 (9/17) (29.2, 76.7)	75.0 (6/8) (45.0, 105.0)	22.1 (-16.2, 60.3)	29.4 (5/17) (7.8, 51.1)	62.5 (5/8) (29.0, 96.0)	33.1 (-6.8, 73.0)
Week 104	Overall	37.8 (56/148) (30.0, 45.7)	58.5 (24/41) (43.5, 73.6)	20.7 (3.7, 37.7)	28.4 (42/148) (21.1, 35.6)	31.7 (13/41) (17.5, 46.0)	3.3 (-12.7, 19.3)
	Moderate PDR or Better (\leq Level 65)	29.9 (29/97) (20.8, 39.0)	40.0 (8/20) (18.5, 61.5)	10.1 (-13.2, 33.4)	25.8 (25/97) (17.1, 34.5)	25.0 (5/20) (6.0, 44.0)	-0.8 (-21.7, 20.1)
	High-risk PDR or worse (\geq Level 71)	52.9 (27/51) (39.2, 66.6)	76.2 (16/21) (58.0, 94.4)	23.2 (0.5, 46.0)	33.3 (17/51) (20.4, 46.3)	38.1 (8/21) (17.3, 58.9)	4.8 (-19.7, 29.2)
	High-risk PDR (71A - 71D)	58.8 (20/34) (42.3, 75.4)	69.2 (9/13) (44.1, 94.3)	10.4 (-19.6, 40.5)	38.2 (13/34) (21.9, 54.6)	23.1 (3/13) (0.2, 46.0)	-15 (-43.3, 13.0)
	High-risk PDR or worse (\geq Level 75)	41.2 (7/17) (17.8, 64.6)	87.5 (7/8) (64.6, 110.4)	46.3 (13.6, 79.1)	23.5 (4/17) (3.4, 43.7)	62.5 (5/8) (29.0, 96.0)	39.0 (-0.2, 78.1)

Table 30: Baseline DRSS: Protocol S Study
(ITT Population)

Baseline DRSS	PRP			Ranibizumab		
	Overall (N=203)	DME (N=46)	No DME (N=157)	Overall (N=191)	DME (N=42)	No DME (149)
14A-14C, 14Z, 15, 20 (DR questionable, microaneurysms only)	1 (0.5)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
35A-35F (mild NPDR)	4 (2.0)	0 (0.0)	4 (2.5)	6 (3.1)	0 (0.0)	6 (4.0)
43A, 43B (moderate NPDR)	5 (2.5)	2 (4.3)	3 (1.9)	2 (1.0)	1 (2.4)	1 (0.7)
47A-47D (moderately severe NPDR)	15 (7.4)	1 (2.2)	14 (8.9)	10 (5.2)	2 (4.8)	8 (5.4)
53A-53E (severe NPDR)	1 (0.5)	1 (2.2)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.7)
60 (prior PRP; without active PDR)	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
61A, 61B (mild PDR)	31 (15.3)	6 (13.0)	25 (15.9)	30 (15.7)	5 (11.9)	25 (16.8)
65A-65C (moderate PDR)	67 (33.0)	15 (32.6)	52 (33.1)	68 (35.6)	12 (28.6)	56 (37.6)
71A-71D (high-risk PDR)	53 (26.1)	15 (32.6)	38 (24.2)	47 (24.6)	13 (31.0)	34 (22.8)
75 (high-risk PDR)	20 (9.9)	4 (8.7)	16 (10.2)	22 (11.5)	8 (19.0)	14 (9.4)
81 (advanced PDR, macula center attached)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (1.3)
85 (advanced PDR, macula center detached)	1 (0.5)	0 (0.0)	1 (0.6)	1 (0.5)	0 (0.0)	1 (0.7)
90 (missing or cannot grade)	4 (2.0)	1 (2.2)	3 (1.9)	2 (1.0)	1 (2.4)	1 (0.7)

Table 31: Baseline DRSS: Pooled RISE/RIDE Studies
(Randomized Subjects with DR Severity Evaluation at Baseline)

Baseline DRSS	Sham (N=254)	Ranibizumab 0.3 mg (N=245)	Ranibizumab 0.5 mg (N=247)
10, 12 (DR absent)	1 (0.4%)	1 (0.4%)	1 (0.4%)
14A-14C, 14Z, 15, 20 (DR questionable, microaneurysms only)	3 (1.2%)	3 (1.2%)	3 (1.2%)
35A-35F (mild NPDR)	38 (15.0%)	39 (15.9%)	42 (17.0%)
43A, 43B (moderate NPDR)	33 (13.0%)	29 (11.8%)	34 (13.8%)
47A-47D (moderately severe NPDR)	72 (28.3%)	74 (30.2%)	64 (25.9%)
53A-53E (severe NPDR)	14 (5.5%)	14 (5.7%)	10 (4.0%)
60, 61A, 61B (mild PDR)	64 (25.2%)	64 (26.1%)	69 (27.9%)
65A-65C (moderate PDR)	12 (4.7%)	7 (2.9%)	9 (3.6%)
71A-71D (high-risk PDR)	2 (0.8%)	3 (1.2%)	1 (0.4%)
75 (high-risk PDR)	0 (0.0%)	0 (0.0%)	1 (0.4%)
90 (cannot grade)	15 (5.9%)	11 (4.5%)	13 (5.3%)

Reviewer analysis: derived from individual study summaries of the RISE and RIDE studies presented in Table 3 of statistical review.

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/s/

SOLOMON CHEFO
03/24/2017

YAN WANG
03/24/2017

I concur with the overall conclusions.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

OTHER REVIEW(S)

**Division of Transplant and Ophthalmology Products
Associate Director for Labeling Recommendations
of the Prescribing Information**

Product Title	Lucentis (ranibizumab)
Applicant	Genentech
Application/Supplement Number	114
Type of Application/Submission	Efficacy Supplement
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Approved Indications	<ul style="list-style-type: none"> • Neovascular (wet) age-related macular degeneration • Macular edema following retinal vein occlusion • Diabetic macular edema (DME) • Diabetic retinopathy in patients with DME • Myopic choroidal neovascularization (mCNV)
Proposed Indication	Treatment of diabetic retinopathy (i.e., independent of diabetic macular edema status)
Date FDA Received Application	October 18, 2016
Review Classification (Priority/Standard)	Standard
Action Goal Date	April 18, 2017
Review Date	03/ 29/ 2017
Reviewer	Jane Filie, MD

This Associate Director for Labeling (ADL) memorandum provides recommendations for consideration by the management of the Division of Transplant and Ophthalmology Products, on the content and format of the prescribing information (PI) to help ensure that the PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements¹
- Is consistent with labeling guidance recommendations² and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

¹ See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR [201.56\(e\)](#) and [201.80](#).

²See [PLR Requirements for PI](#) website for PLR labeling guidances.

The applicant submitted an efficacy supplement seeking to include the indication for the treatment of diabetic retinopathy (i.e., independent of diabetic macular edema status).

During the review of the label it was noted that the current established pharmacological class in the currently approved label is not according to the publicly available FDA list of established pharmacological class phrases (FDA EPC list). The current label refers to ranibizumab as “vascular endothelial growth factor (VEGF) inhibitor”, whereas the FDA EPC list describes it as “vascular endothelial growth factor-directed antibody”. Ranibizumab is not an antibody, but an IgG1 kappa fragment (the Fab monoclonal antibody fragment which lacks an Fc region) which binds and inhibits the biological activity of VEGF-A, therefore describing ranibizumab as an antibody would be a misnomer. Based on discussions with the nonclinical and clinical supervisors the current term will remain on the label based on the rationale that the current EPC term describes more appropriately the mechanism of action of the drug for the ophthalmic indications. The inclusion of the term “vascular endothelial growth factor (VEGF) inhibitor” to the FDA EPC list is being requested to the National Drug File Reference Terminology Group, through Dr. Paul Brown who is currently the designated staff member in charge of updating the pharmacologic class structured product labeling as per the MaPP 7400.13 Determining the Established Pharmacologic Class for Use in the Highlights of Prescribing Information and guidance for industry “Labeling for Human Prescription Drug and Biological Products- Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information”. See electronic communication attached in the Appendix.

In the attached PI, the ADL recommendations are presented in track changes (dark orange) throughout the working version of the applicant’s draft PI and comments (in balloons) begin with the bolded acronym “ADL”. This version of the PI includes preliminary changes proposed by the clinical team. In order to preserve the comments within each heading in a sequential order, the amended label attached may not reflect the final formatting of the label.

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/s/

JANE FILIE
04/11/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 20, 2017

To: Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA: 125156**
LUCENTIS[®] (ranibizumab injection)

On January 12 and March 17, 2017, DTOP consulted OPDP to review the proposed package insert (PI) and carton and container labeling, respectively, for LUCENTIS[®] (ranibizumab injection).

OPDP reviewed the proposed substantially complete version of the PI located in SharePoint on March 17, 2017 (entitled, "1-13-17 redlined-label-text"). OPDP's comments are provided in the attached version of the substantially complete labeling.

OPDP has reviewed the carton and container labeling, located in SharePoint on March 17, 2017 (entitled "draft-cart-cont-labels-12-6", also attached), and we do not have any comments.

Thank you for your consult. If you have any questions regarding these comments, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
03/20/2017

Clinical Inspection Summary

Date	March 9, 2017
From	Roy Blay, Ph.D., Reviewer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief, Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lois Almoza\Project Manager Rhea Lloyd\Medical Officer William Boyd\ Team Leader Division of Transplantation and Ophthalmic Products (DTOP)
NDA/BLA #	BLA 125156/S-114
Applicant	Genentech, Inc.
Drug	Lucentis® (ranibizumab injection)
NME (Yes/No)	No
Therapeutic Classification	Priority Review
Proposed Indication(s)	Treatment of Diabetic Retinopathy (DR)
Consultation Request Date	November 29, 2016
Summary Goal Date	March 15, 2017 (previously extended from Mar 1 and Mar 8, 2017)
Action Goal Date	April 1, 2017
PDUFA Date	April 18, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Dr. Browning's clinical site was inspected in support of this BLA supplement. The pending classification of the inspection of Dr. Browning is No Action Indicated (NAI).

Classification is pending at this site because the reading process(es) used for determining optical coherence tomography (OCT) values are not well defined in the protocol and there are apparent discrepancies between the eCRF (clinical site source data) and data listings provided by the sponsor. The sponsor's listing reportedly reflects central reading facility values. The discrepancies between these readings are presently unexplained (see the table on Page 3).

These discrepancies have been discussed with DTOP who in turn is formally communicating with the sponsor to determine the basis for these discrepancies.

Notwithstanding the concerns regarding the discrepant OCT results, the results of the clinical investigator inspection indicate that Dr. Browning's study conduct appears to have been adequate, and the data otherwise generated by this site appear acceptable in support of the respective indication.

2. BACKGROUND

The Applicant submitted this BLA to support the use of Lucentis® (ranibizumab injection) in the treatment of Diabetic Retinopathy (DR). Protocol ML27976, entitled "Prompt Panretinal

Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy” was inspected in support of this application.

Protocol ML27976

The primary objective of this protocol was to determine if visual acuity outcomes at 2 years in eyes with proliferative diabetic retinopathy (PDR) that received anti-vascular endothelial growth factor (VEGF) therapy with deferred panretinal photocoagulation (PRP) were non-inferior to those in eyes that received standard prompt PRP therapy. The study was designed as a Phase 3, prospective, multi-center randomized clinical trial. Study eyes were assigned randomly (1:1) to either prompt PRP or intravitreal 0.5 mg ranibizumab with deferred PRP. Study subjects with two study eyes received prompt PRP in one eye and ranibizumab with deferred PRP in the other eye.

Protocol ML27976 was conducted at 57 clinical sites in the U.S. Planned enrollment was a minimum of 380 eyes with 394 eyes actually randomized to study. The primary efficacy outcome was the mean change in best corrected visual acuity (BCVA) from baseline to 2 years. The sponsor concluded that the BCVA change at 2 years from baseline demonstrated a greater improvement in the ranibizumab group as compared with the PRP group.

Dr. Browning’s site was selected for inspection because of its enrollment of a relatively large numbers of subjects.

3. RESULTS (by site):

Site #/ Name of CI Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
44/ David J. Browning, M.D., Ph.D. Charlotte Eye, Ear, Nose & Throat Associates, PA 6035 Fairview Road Charlotte, NC 28210-3256	ML27976/ 22	17-19 Jan 2017	NAI. Pending final classification.

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. David Browning, M.D., Ph.D.

At this site for Protocol ML27976, 23 subjects were screened, and from 22 eligible subjects, 29 eyes were randomized. Of the 29 randomized eyes, 22 eyes completed the study with four eyes lost to follow-up prior to the Week 104 visit, and two subjects (3 randomized eyes) who died prior to study completion at Week 104. Subject (b) (6) in the PRP group died of renal failure, and Subject (b) (6) in the bilaterally treated group died of congestive heart failure. In neither case was the subject's outcome considered related to study drug treatment.

All 23 screened subjects were consented appropriately prior to the conduct of any study-related procedures. All subject data was entered directly into electronic Case Report Forms (eCRFs). Records reviewed included IRB approvals of the protocol, informed consent documents, protocol amendments, progress notes, adverse event reports, deviation reports, and annual study approvals. Other records included, but were not limited to, financial disclosure, monitoring reports, inclusion/exclusion criteria, study procedures, the primary efficacy endpoint, adherence to the study protocol, and drug accountability.

The study records for all 29 randomized eyes were reviewed for adverse events, concomitant medications, and efficacy. The records of nine of 22 subjects were reviewed for inclusion/exclusion criteria, study procedures, and protocol adherence. Source documents were compared with the eCRFs and the data in the provided line listings. No discrepancies were noted. The primary efficacy endpoint was the change in visual acuity from baseline to 2 years. This data was contained in Listing H and was confirmed for every study subject. OCT values were determined by the site and entered into the eCRFs. The OCT report was then sent to the reading center which determined its own value. Diabetic retinopathy (DR) scores were assigned by the reading center. The reading center OCT values occasionally differed from that of the site; for example:

Subject/visit/eye/ Treatment	Value on data listing/Values by Reading Center	Value in eCRF	Difference
(b) (6)/baseline/L/ ranibizumab	208	215	-7
(b) (6)/baseline/L ranibizumab	184	203	-19
(b) (6)/baseline/R/ PRP	319	315	+4
(b) (6)/baseline/R/ PRP	222	217	+5
(b) (6)/Week 104/L/ ranibizumab	251	255	-4
(b) (6)/Week 104/L PRP	326	347	-21
(b) (6)/Week 104/R/ PRP	267	263	+4
(b) (6)/Week 104/R/ PRP	149	224	-75

The data listings provided by the sponsor were reportedly those values determined by the reading center. These values were not reported back to the study site. According to the study site, a review committee monitored differences in values assigned by the study site and the reading center. Unusual differences would be investigated and additional training would be provided to the sites and/or reading center as needed. For this study, the differences in values between those determined by the study site and the reading center were not considered unusual.

A Form FDA 483 was not issued at the conclusion of the inspection. Notwithstanding the discrepant OCT results, the results of the clinical investigator inspection indicate that Dr. Browning's study conduct appears to have been adequate, and the data otherwise generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.\ BLA 125156/S-114
DTOP\Division Director\Renata Albrecht
DTOP\Team Leader\William Boyd
DTOP\Medical Officer\Rhea Lloyd
DTOP\Project Manager\Lois Almoza
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
03/09/2017

JANICE K POHLMAN
03/09/2017

KASSA AYALEW
03/10/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 6, 2017

Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)

Application Type and Number: BLA-125156/S-114

Product Name and Strength: Lucentis
(ranibizumab injection)
0.3 mg and 0.5 mg single-use vials

Submission Date: October 18, 2016

Applicant/Sponsor Name: Genentech, Inc.

OSE RCM #: 2017-66

DMEPA Primary Reviewer: Madhuri R. Patel, PharmD.

DMEPA Team Leader (Acting): Sarah K. Vee, PharmD.

1 PURPOSE OF MEMO

Division of Transplant and Ophthalmology Products (DTOP) requested that we review the revised the proposed container label, carton labeling, and Prescribing Information (PI) for Lucentis (ranibizumab injection) (BLA 125156/S-114) (Appendix A) to determine if it is acceptable from a medication error perspective. Genentech submitted a Prior Approval Supplement (PAS) on October 18, 2016 which proposes a revision to the indication of diabetic retinopathy (DR) in patients with diabetic macular edema (DME) to include all diabetic retinopathy patients independent of diabetic macular edema status. Genentech submitted updated label and labeling on December 6, 2016 and January 13, 2017, which incorporated changes approved for Lucentis Prior Approval Supplement BL 125156/S-112 and 125156/S-111, respectively. The updates are in response to recommendations that we made during a previous label and labeling review.^a

^a Patel M. Label and Labeling Review for Lucentis (BLA 125156/S-111 & 112). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 NOV 04. 17 p. OSE RCM No.: 2016-2039 and 2016-1678.

2 CONCLUSION

The proposed container label, carton labeling, and Prescribing Information (PI) is acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

MADHURI R PATEL
03/06/2017

SARAH K VEE
03/06/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s114

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



BLA 125156

MEETING MINUTES

Genentech, Inc.
Attention: Clara Cambon, Pharm.D.
Regulatory Program Management
1 DNA Way, Bldg 35, MS 5F
South San Francisco, CA 94080-4990

Dear Dr. Cambon:

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 telecon between representatives of your firm and the FDA on December 15, 2015. The purpose of the meeting was to discuss the proposed content, analyses and structure of a sBLA to support the inclusion of a new indication for the treatment of myopic choroidal neovascularization (mCNV) in the Lucentis prescribing information on the basis of the single Phase 3 study CRFB002F2301 (RADIANCE).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-sBLA

Meeting Date and Time: December 15, 2015 from 1:00PM -2:00PM
Meeting Format: Teleconference

Application Number: 125156
Product Name: Lucentis (ranibizumab injection)
Indication: Treatment of myopic choroidal neovascularization
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Christina Marshall, MS

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
Solomon Chefo, Biostatistics Reviewer
Yan Wang, Biostatistics Team Leader
Christina Marshall, Regulatory Health Project Manager

Genentech, Inc. ATTENDEES

Ronald Cantrell, Principal Real World Data Scientist
Steven Francom, Senior Statistical Scientist, Biostatistics, Product Development
Susanna Grzeschik, Safety Science Leader, Safety Science
Zdenka Haskova, Associate Medical Director, Clinical Ophthalmology
Clara Cambon, Regulatory Project Management
Hilary Henshaw, Program Director, Regulatory
Jill Hopkins, Associate Group Medical Director, Clinical Ophthalmology
Jane Ives, Senior Clinical Development Scientist, Clinical Science
Rachna Mittal, Project Lead Senior Statistical Programming and Analysis, Product Development Biometrics
Natasha Singh, Lucentis Global Development Team Leader
Jiameng Zhang, Principal Statistical Scientist, Biostatistics, Product Development

BACKGROUND

Genentech, Inc. is proposing to file a sBLA to support the use of Lucentis (ranibizumab injection) in the treatment of myopic choroidal neovascularization (mCNV) on the basis of the Phase 3 RADIANCE (RFB002F2301) study conducted by Novartis.

Genentech, Inc. had requested this Type B to discuss the proposed content, analyses and structure of a sBLA to support the inclusion of a new indication for the treatment of mCNV in the Lucentis prescribing information on the basis of the single Phase 3 study CRFB002F2301 (RADIANCE). Preliminary responses to the questions posted in the briefing document dated November 13, 2015, were sent on December 8, 2015. Genentech, Inc. provided via email on December 8, 2015, acceptance of the Division's responses, but requested additional clarifying information on questions 1-4.

For the purposes of these minutes, the questions posted by the applicant in the briefing documents 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 efficacy and safety data from the single Phase III study (RADIANCE–CRFB002F2301) are sufficient to support the proposed sBLA to include the treatment of mCNV as a new indication in the Lucentis prescribing information?

FDA Response:

It is not possible to tell whether study (RADIANCE–CRFB002F2301) would support the approval of an additional indication in patients with myopic choroidal neovascularization. The study report does not include sufficient details to evaluate the study; however, there are a number of potential issues which may influence the utility of the study. These issues include: 1) the study is not adequately controlled after month 3; 2) the study report does not define "stabilization" which limits the opportunity to identify how treatment decisions were made; 3) the retreatment criteria appears to have an impact on the number of injections given but not on the visual function (Figure 1).

Meeting Discussion:

The Division questioned the 3 month study design and asked for clarification on the number of injections at different time points. Genentech acknowledged that patients in the ranibizumab-treated arms required different number of injections to achieve visual benefit, some requiring 1-3 total injections and others requiring more. The Division stated that regardless of the differing number of injections, the visual outcomes in the two ranibizumab groups were the same, raising questions about the contribution of each injection. Genentech confirmed that they would take this approach into consideration in the preparation of the submission and confirmed that the key efficacy analysis would be performed based on BCVA outcome at Month 3.

Question 2

Does the Division agree that the primary endpoint used in RADIANCE (the change in BCVA from baseline averaged over Months 1, 2, and 3), further supported by pre-specified secondary endpoints at Month 6 and Month 12, including the mean BCVA change at 12 months from baseline, represent substantial evidence to demonstrate the treatment benefit of Lucentis to support review of an sBLA for mCNV?

FDA Response:

No, the Division disagrees with the primary efficacy endpoint used in the RADIANCE study i.e., the change in best corrected visual acuity (BCVA) averaged over Months 1, 2, and 3. The determination of which data may provide substantial evidence to demonstrate a treatment benefit of Lucentis for the proposed indication would require submission and review of the data.

Meeting Discussion:

Genentech asked what would be a preferred primary endpoint. The Division informed Genentech that monthly BCVA analyses were preferred. Division inquired about the rationale for proposing the primary endpoint used in RADIANCE. Genentech noted that the trial design had been developed by Novartis and that they would follow-up with Novartis to provide additional information to the Agency on the choice of this endpoint. Genentech asked if the three efficacy analyses: mean change in BCVA from baseline at Month 3, mean change in BCVA from baseline at each study visit (Month 1 through Month 12), and categorized BCVA gains: proportion of subjects with a BCVA improvement of at least 15 letters from baseline at each study visit (Month 1 through Month 12) would be acceptable. The Division agreed.

Question 3

Genentech proposes a dosing regimen for mCNV with Lucentis treatment based on BCVA stability guided criteria. Is this acceptable to the Division?

FDA Response:

No. See response to Question 1.

Meeting Discussion:

Genentech asked the Division of their thoughts on an acceptable dosing regimen. The Division noted that there seemed to have been more injections given to patients in the group that received ranibizumab guided by stabilization criteria compared to the ranibizumab group guided by disease activity. The Division questioned whether the investigator's discretion could introduce bias after the 3-month controlled period. Genentech asked whether a recommended dosing regimen of three monthly doses could be accepted by the Agency. The Division invited Genentech to put forward their best proposal in their submission and concluded that the Agency would review any proposal in light of all available data. Genentech asked whether there would be any other analyses that the Agency would find important in the filing. The Division recommended including efficacy analyses by injection number. Genentech agreed to provide new analysis for the first three months.

Question 4

Does the Division agree with the proposed mCNV sBLA content and structure (Section 12 and Appendix 2)? Specifically:

a) Does the Division agree the original CSR, Summary of Efficacy, and Summary of Safety documents written by Novartis (Sponsor of the study), and containing Novartis analyses are acceptable to support the review of an application?

FDA Response:

No, while the original CSR, Summaries of Efficacy and Summary of Safety documents should be submitted in support of a sBLA, they do not provide sufficient information to complete a review. The Division suggests in addition, that the original protocol together with any amendments, the original statistical analysis plan and any amendments, full raw data and analysis sets, the 95% confidence interval and p-values for the treatment difference in mean change in BCVA and the proportion of subjects with a BCVA improvement of at least 15 letters, at each study visit (Month 1 through Month 12) be submitted to support the review.

In addition, we have the following question, in the statistical section of the CSR you indicated that stratification was done based on categories of baseline BCVA: ≤ 60 letters vs > 60 letters. It is not clear to us if this stratification factor was used during randomization. Please clarify.

Meeting Discussion:

None

b) Does the Division agree that the raw datasets and analysis datasets produced by Novartis are acceptable for sBLA review (Section 12.2)?

FDA Response:

You indicated that the datasets are not in CDISC format. Although non-CDISC format datasets are acceptable, we recommend that you submit the dataset using CDISC format. We also recommend that you submit all the programming codes (with clear documentations) that were used to generate the efficacy and safety results presented in the clinical study reports.

Meeting Discussion:

Genentech asked if submitting read-only programs would be acceptable to the Agency. The Division asked for clarification on this type of program. Genentech clarified the Agency will be able to run their own programs on the datasets, as usual. The Division accepted their proposal. Genentech confirmed that the read-only programs and accompanying documentation would be submitted for the three key efficacy analyses:

- Mean change in BCVA from baseline at Month 3,
- Mean change in BCVA from baseline at each study visit (Month 1 through Month 12),
- Categorized BCVA gains: proportion of subjects with a BCVA improvement of at least 15 letters from baseline at each study visit (Month 1 through Month 12).

Genentech also stated that they are willing to provide read-only programs for the frequency tables for ocular and non-ocular adverse events (AEs) and serious adverse events (SAEs). The Division accepted this proposal.

Question 5

Does the Division agree with the proposed plan to not submit a 120-day/90-day safety update given RADIANCE has been completed (no new data anticipated) and safety data observed is consistent with the established Lucentis safety profile (Section 12.4)?

FDA Response:

Disagree. A 120-day safety update should be submitted documenting if there is any new safety data not submitted to the Lucentis BLA in routine safety reporting.

Meeting Discussion:

None

Question 6

Does the Division have any other comments with respect to the proposed sBLA?

FDA Response:

None at this time.

Meeting Discussion:

None

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

The Division will issue the meeting minutes within 30 days

ATTACHMENTS AND HANDOUTS

None

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
01/11/2016