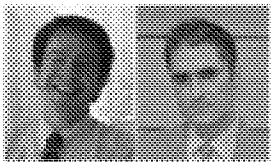
presented by Ophthalmology Management

AMD Update

June 2010, Issue 42

The "Treat and Extend" Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration

Michael Engelbert, MD
K. Bailey Freund, MD
Edward S. Harkness Eye Institute, Columbia University College of Physicians & Surgeons, New York, NY,
Vitreous-Retina-Macula Consultants of New York, New York, NY
LuEsther T. Mertz Retinal Research Center, New York, NY
This work is supported by The Macula Foundation, Inc..

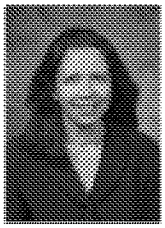


While monthly injections of intravitreal anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (AMD) have produced visual outcomes superior to prior therapies,[1,2] the frequency of office visits and injections can place a tremendous burden on patients and the health care system. Unfortunately, the PIER trial,[3] which is the only randomized, double-blind, sham-controlled trial investigating a less frequent dosing regimen, yielded inferior visual outcomes compared to outcomes reported after monthly dosing. Patients in the PIER trial were examined and treated quarterly following an initial series of three monthly injections. The open-label, non-randomized PrONTO study also employed three initial monthly injections but was followed by "as needed" dosing based on changes in visual acuity, clinical findings and optical coherence tomography (OCT) evaluation.[4,5] The PrONTO regimen appeared to achieve visual results similar to monthly dosing with fewer injections, but patients still required monthly visits, examinations, and OCTs. Furthermore, after the initial mandated series of three injections, this protocol allowed fluid to re-accumulate at the fovea before treatment was repeated, raising concerns regarding incremental long-term vision loss and the possibility of new hemorrhages during periods without VEGF inhibition.[6,7,8]

The "Treat and Extend" dosing regimen is a tailored maintenance regimen intended to achieve optimal visual results with two additional goals.[9] Like PIER and PrONTO, it consists of at least three initial monthly injections, but, once stable visual acuity, an absence of macular hemorrhage, and a dry OCT have been achieved, patients continue to receive regular maintenance injections at increasing intervals. Once stability is achieved with monthly dosing, the patient is instructed to return in six weeks. Visual acuity, clinical findings, and OCT changes are recorded again and patients receive an injection regardless of the presence or absence of disease activity. However, the interval to the next visit (and scheduled injection) is based on an observed change in the above parameters. If there are no changes, the interval to the next visit is extended to seven or eight weeks (hence the term "Treat and Extend"). However, if there is evidence of renewed disease activity, the interval for the next scheduled injection and examination is shortened. In our own clinical practice, we rarely extend the interval between injections and examination beyond 8-9 weeks.

One goal of "Treat and Extend" is to reduce the treatment burden by reducing number of patient visits and the number of imaging studies performed by eliminating the need for the monthly visits necessitated by alternative dosing strategies. We recently reported success in achieving this goal in two small cohorts of eyes with newly diagnosed type 1 (occult)[10] and type 3 (retinal angiomatous proliferation)[11] neovascularization. In these reports, the eyes with type 3 vessels had a sustained visual improvement of approximately 2 Snellen

Ingrid U. Scott, MD, MPH, Editor



Professor of Ophthalmology and Public Health Sciences,
Penn State College of Medicine

PRINT FRIENDLY VERSION
FORWARD TO COLLEAGUE
NEWSLETTER ARCHIVE
AMD UPDATE WEBSITE

lines while the eyes with type 1 vessels achieved visual stabilization. The number of office visits and injections was reduced by 25-50% compared to a monthly dosing regimen.

A second goal of the "Treat and Extend" dosing regimen is to reduce the risk of new sight-threatening submacular hemorrhages. We recently demonstrated a statistically significant increase in macular hemorrhages when patients in the PIER trial were switched from a monthly to quarterly dosing regimen.[6] Unfortunately, large and potentially devastating submacular hemorrhages may occur almost immediately after a high-quality OCT examination showing an absence of fluid.[7, 8] Theoretically, eyes treated with an OCT-guided "as needed" regimen, in which patients may go long intervals without VEGF suppression, could be at a greater risk for sight-threatening submacular hemorrhages compared to eyes receiving more frequent and regular anti-VEGF treatments. In our two retrospective series, we did not observe any sight-threatening macular hemorrhages. Also, unlike the ANCHOR, MARINA and PrONTO studies which are limited to 24 months of follow-up, 17 of our 28 patients completed 36 month follow-up. We are not aware of any other dosing regimen of anti-VEGF therapy that has demonstrated stable or improved VA out to three years.

While initial results of the "Treat and Extend" dosing regimen appear promising, the strategy requires further validation in a larger randomized trial. Clinicians should view the current data regarding different regimens critically when deciding which dosing strategy is best for individual patients.

REFERENCES

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006; 355: 1419-31
2. Brown DM, Kaiser PM, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engel J Med 2006; 355: 1432-1444
3. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. Feb 2008;145(2):239-248.
4. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol. Apr 2007;143 (4):566-583.
5. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 2009 Jul;148(1):43-58.e1. Epub 2009 Apr 18.
6. Barbazetto I, Saroj N, Freund KB. Dosing regimen and the frequency of macular hemorrhages in neovascular age-related macular degeneration treated with ranibizumab. Presented at the Annual Meeting of the Retina Society, September 2008.
7. Margolis R, Freund KB. Hemorrhagic recurrence of neovascular age-related macular degeneration not predicted by spectral domain optical coherence tomography. Retinal Cases and Brief Reports, in press.
8. Levine JP, Marcus I, Sorenson JA, Spaide RF, Cooney MJ, Freund KB. Macular hemorrhage in neovascular age-related macular degeneration after stabilization with antiangiogenic therapy. Retina. 2009 Sep;29(8):1074-9.
9. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am J Ophthalmol. 2007 Apr;143(4):679-80.
10. Engelbert M, Zweifel SA, Freund KB. Long-term Follow-up for Type 1 (sub-RPE) Neovascularization using a "Treat and Extend" Dosing Regimen of Intravitreal Anti-vascular Endothelial Growth Factor Therapy". Retina, accepted for publication.
11. Engelbert M, Zweifel SA, Freund KB. "Treat and extend" dosing of intravitreal antivascular endothelial growth factor therapy for type 3 neovascularization/retinal angiomatous proliferation. Retina. 2009 Nov-Dec;29(10):1424-31.

Erratum

We apologize that last month's article, *Comparison of Two Doses of Intravitreal Bevacizumab as Primary Treatment for Subfoveal CNV Associated with AMD at 24 Months: The Pan-American Collaborative Retina Study Group* by J. Fernando Arevalo, MD, FACS and Martin A. Serrano, MD was originally scheduled for a later issue but was in error released in May 2010.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA® (aflibercept) Injection, for Intravitreal Injection
Initial U.S. Approval: 2011

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

• Dosage and Administration (2)	8/2018
• Warnings and Precautions, Thromboembolic Events (5.3)	8/2018

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

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor 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) in Patients with DME (1.4)

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

- **Neovascular (Wet) Age-Related Macular Degeneration (AMD)**
  - The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
  - Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)
    Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.
- **Macular Edema Following Retinal Vein Occlusion (RVO)**
  - The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). (2.3)
- **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema**
  - The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
  - Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

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

Injection: 2 mg/0.05 mL solution for intravitreal injection in a single-dose vial (3)

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

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

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

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

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

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of:

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) in Patients with DME

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

A 5-micron sterile filter needle (19-gauge × 1½-inch), a 1-mL Luer lock syringe and a 30-gauge × ½-inch sterile injection needle are needed.

EYLEA is available packaged as follows:

- Vial Only
- Vial Kit with Injection Components (filter needle, syringe, injection needle)

[*see How Supplied (16)*].

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

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.1)*]. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly) [*see Clinical Studies (14.2), (14.3)*].

2.4 Diabetic Macular Edema (DME)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.4)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.5)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

The glass vial is for single use only.

EYLEA is available packaged as follows:

- Vial Only
- Vial Kit with Injection Components (filter needle, syringe, injection needle)

[*see How Supplied (16)*].

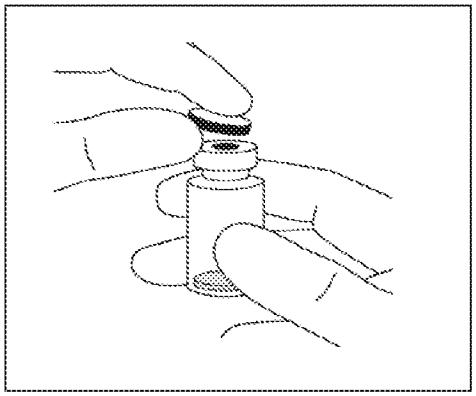
Use aseptic technique to carry out the following preparation steps:

Prepare for intravitreal injection with the following medical devices for single use:

- a 5-micron sterile filter needle (19-gauge × 1½-inch)
- a 1-mL sterile Luer lock syringe (with marking to measure 0.05 mL)
- a sterile injection needle (30-gauge × ½-inch)

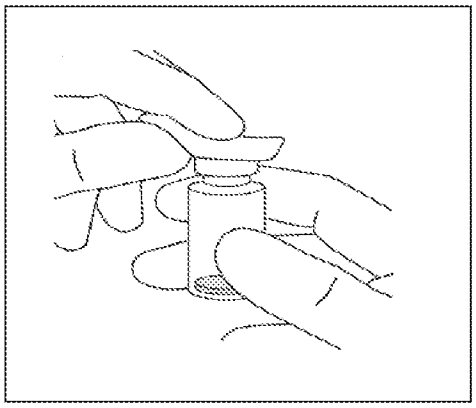
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



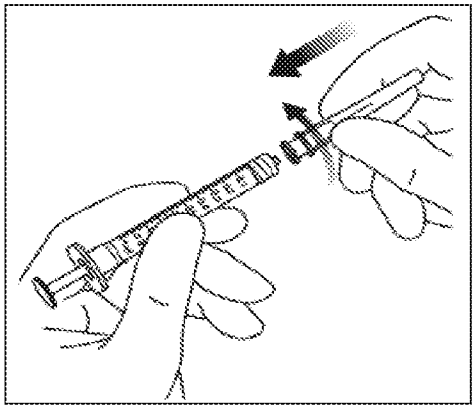
2. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle and the 1-mL syringe from their packaging. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

Figure 3:



4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figures 4a and 4b).

Figure 4a:

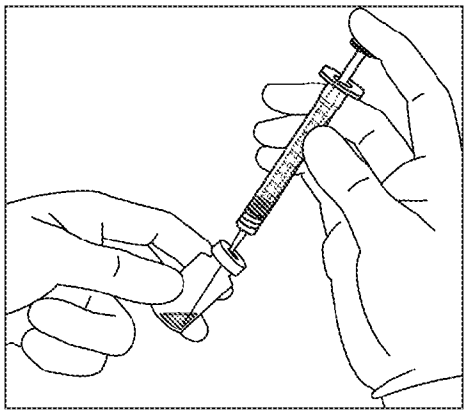
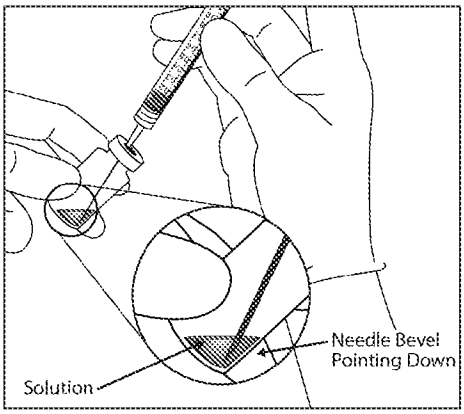
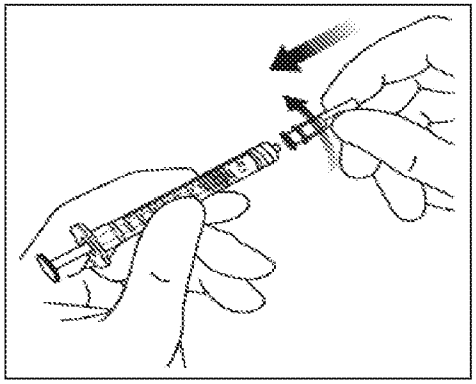


Figure 4b:



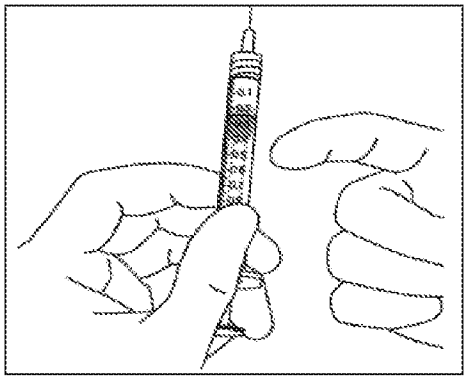
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
7. Remove the filter needle from the syringe and properly dispose of the filter needle.
Note: Filter needle is **not** to be used for intravitreal injection.
8. Remove the 30-gauge x ½-inch injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

Figure 5:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.
10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

Figure 6:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7a and 7b).

Figure 7a:

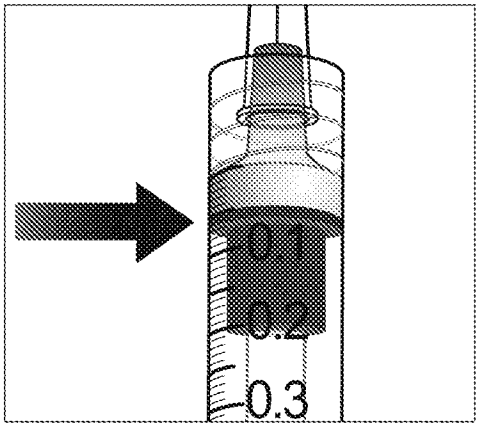
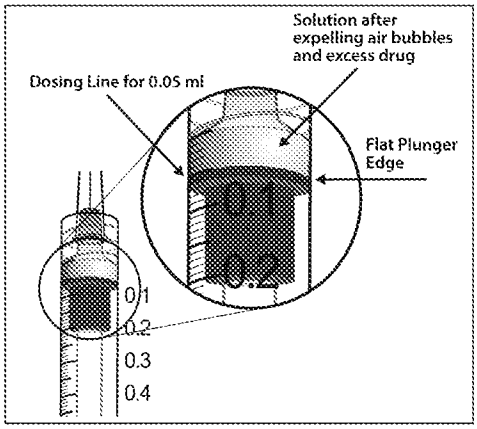


Figure 7b:



2.7 Injection Procedure

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

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (17)*].

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid

speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Injection: 2 mg/0.05 mL clear, colorless to pale yellow solution in a single-dose, glass vial for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

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

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1) [*see Clinical Studies (14.1)*].

Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 96	
	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO)

The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT) [*see Clinical Studies (14.2), (14.3)*].

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME)

The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100 [*see Clinical Studies (14.4)*].

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for

24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal 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 EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug 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, EYLEA is not recommended during breastfeeding.

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

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA (aflibercept) Injection is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution for intravitreal injection in a single-dose, glass vial designed to deliver 0.05 mL (50 microliters) of solution containing 2 mg of EYLEA

(40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

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

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions during the first year.

Macular Edema Following Retinal Vein Occlusion (RVO)

Reductions in mean retinal thickness were observed in COPERNICUS, GALILEO, and VIBRANT at week 24 compared to baseline. Anatomic data were not used to influence treatment decisions [*see Clinical Studies (14.2), (14.3)*].

Diabetic Macular Edema (DME)

Reductions in mean retinal thickness were observed in VIVID and VISTA at weeks 52 and 100 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions [*see Clinical Studies (14.4)*].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, RVO, or DME, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, RVO, and DME, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL), 0.05 mcg/mL (range: 0 to 0.081 mcg/mL), and 0.03 mcg/mL (range: 0 to

0.076 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment

Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients.

Other

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) for free aflibercept that was approximately 1500 times higher than the systemic exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

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

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Protocol-specified visits occurred every 28±3 days. Patient ages ranged from 49 to 99 years with a mean of 76 years.

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 week 52 compared to baseline. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1. Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 4 and Figure 8 below.

Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference[b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference[b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

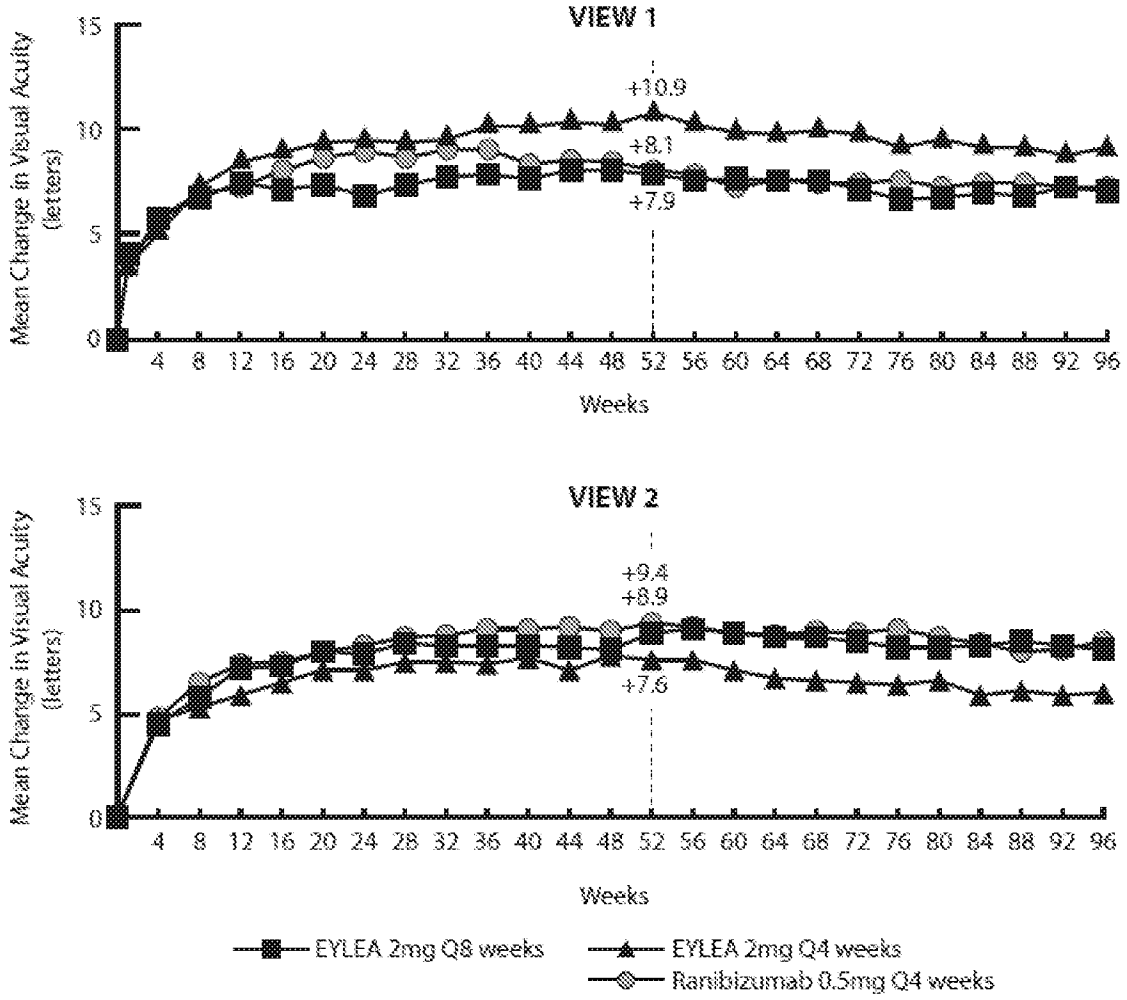
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.

[a] After treatment initiation with 3 monthly doses

[b] EYLEA group minus the ranibizumab group

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity) in each study were in general consistent with the results in the overall populations.

Figure 8: Mean Change in Visual Acuity from Baseline to Week 96* in VIEW1 and VIEW2 Studies



*Patient dosing schedules were individualized from weeks 52 to 96 using a modified 12-week dosing regimen.

VIEW1 and VIEW2 studies were both 96 weeks in duration. However after 52 weeks patients no longer followed a fixed dosing schedule. Between week 52 and week 96, patients continued to receive the drug and dosage strength to which they were initially randomized on a modified 12 week dosing schedule (doses at least every 12 weeks and additional doses as needed). Therefore, during the second year of these studies there was no active control comparison arm.

14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a

3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

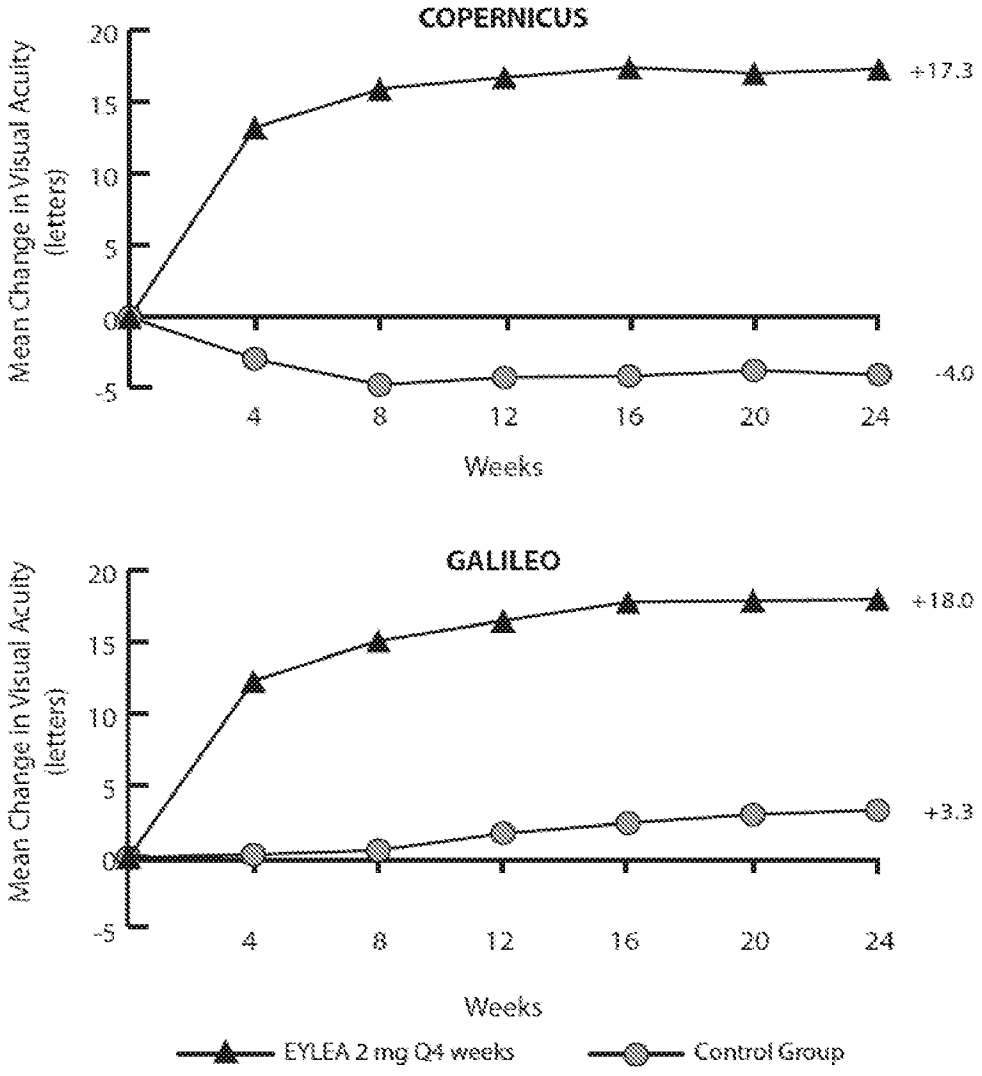
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 9 below.

Table 5: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

	COPERNICUS		GALILEO	
	Control	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q4 weeks
	N=73	N=114	N=68	N=103
Efficacy Outcomes				
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	12%	56%	22%	60%
Weighted Difference [a, b] (%) (95.1% CI)		44.8%[c] (32.9, 56.6)		38.3%[c] (24.4, 52.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.3 (14.1)	18.0 (12.2)
Difference in LS mean [a, d] (95.1% CI)		21.7[c] (17.3, 26.1)		14.7[c] (10.7, 18.7)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study.
[c] $p<0.01$ compared with Control
[d] LS mean and CI based on an ANCOVA model

Figure 9: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies



Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

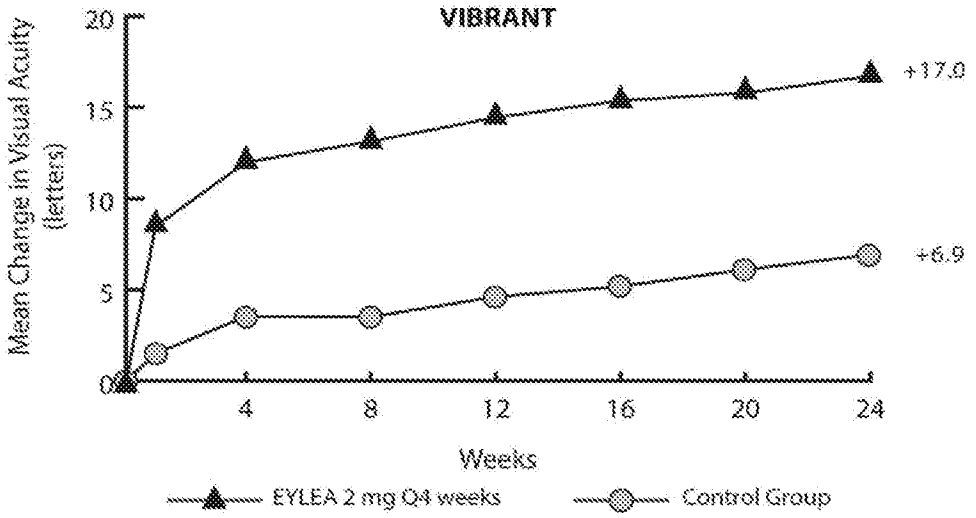
Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 10 below.

Table 6: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

	VIBRANT	
	Control	EYLEA 2 mg Q4 weeks
	N=90	N=91
Efficacy Outcomes		
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	26.7%	52.7%
Weighted Difference [a, b] (%) (95% CI)		26.6%[c] (13.0, 40.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	6.9 (12.9)	17.0 (11.9)
Difference in LS mean [a, d] (95% CI)		10.5[c] (7.1, 14.0)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)
[c] $p<0.01$ compared with Control
[d] LS mean and CI based on an ANCOVA model

Figure 10: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in VIBRANT Study



Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

14.4 Diabetic Macular Edema (DME)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both EYLEA 2Q8 and EYLEA 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.

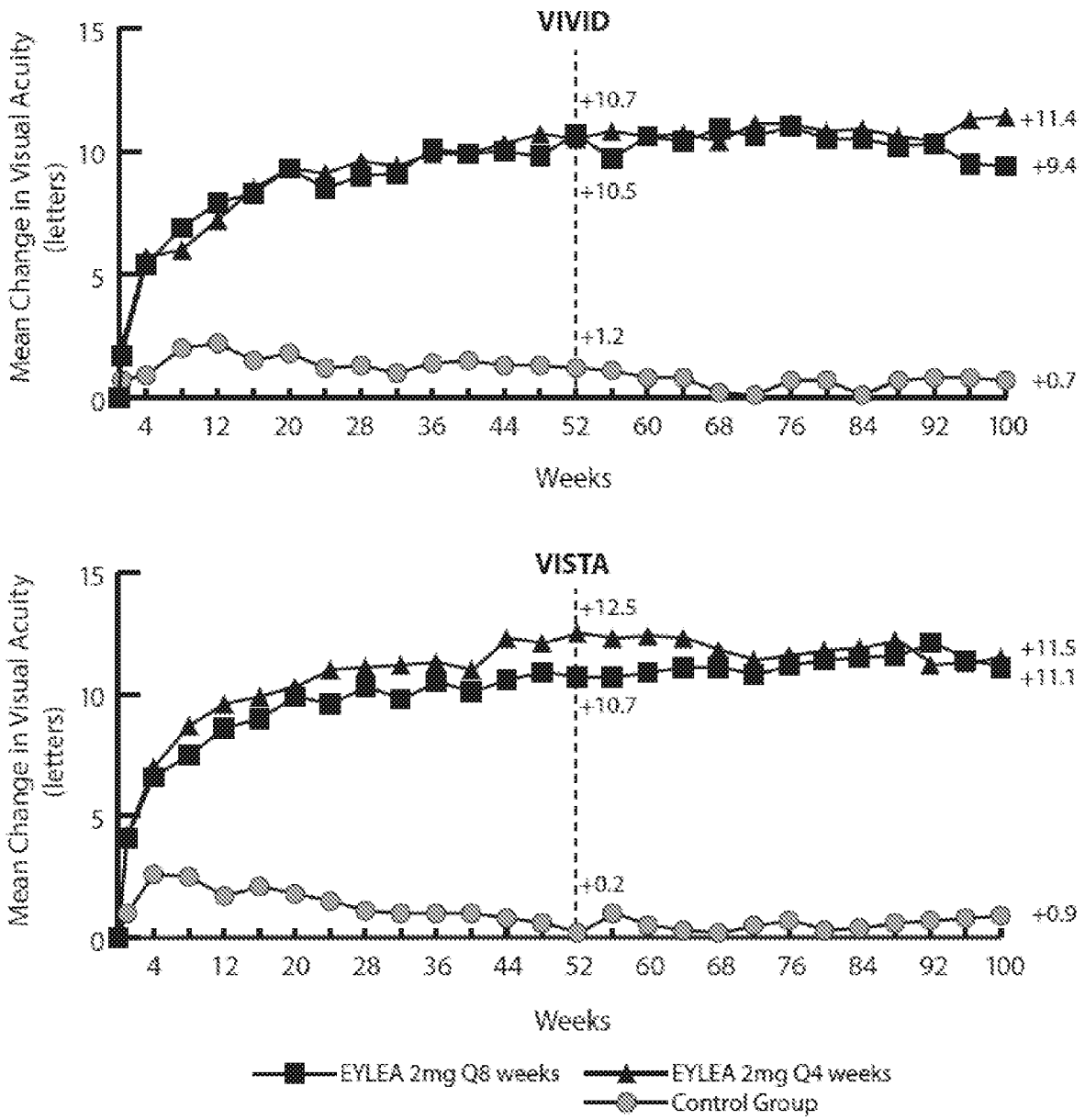
Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 11 below.

Table 7: Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control
Full Analysis Set	N=135	N=136	N=132	N=151	N=154	N=154
Efficacy Outcomes at Week 52						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	10.7 (9.3)	10.5 (9.6)	1.2 (10.6)	10.7 (8.2)	12.5 (9.5)	0.2 (12.5)
Difference[b, c] in LS mean (97.5% CI)	9.1[d] (6.3, 11.8)	9.3[d] (6.5, 12.0)		10.5[d] (7.7, 13.2)	12.2[d] (9.4, 15.0)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	33.3%	32.4%	9.1%	31.1%	41.6%	7.8%
Adjusted Difference[c, e] (%) (97.5% CI)	24.2%[d] (13.5, 34.9)	23.3%[d] (12.6, 33.9)		23.3%[d] (13.5, 33.1)	34.2%[d] (24.1, 44.4)	
Efficacy Outcomes at Week 100						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	9.4 (10.5)	11.4 (11.2)	0.7 (11.8)	11.1 (10.7)	11.5 (13.8)	0.9 (13.9)
Difference[b, c] in LS mean (97.5% CI)	8.2[d] (5.2, 11.3)	10.7[d] (7.6, 13.8)		10.1[d] (7.0, 13.3)	10.6[d] (7.1, 14.2)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	31.1%	38.2%	12.1%	33.1%	38.3%	13.0%
Adjusted Difference[c, e] (%) (97.5% CI)	19.0%[d] (8.0, 29.9)	26.1%[d] (14.8, 37.5)		20.1%[d] (9.6, 30.6)	25.8%[d] (15.1, 36.6)	

[a] After treatment initiation with 5 monthly injections
[b] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model.
[c] Difference is EYLEA group minus Control group
[d] $p<0.01$ compared with Control
[e] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.

Figure 11: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID and VISTA Studies



Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study were in general consistent with the results in the overall populations.

14.5 Diabetic Retinopathy (DR) in Patients with DME

In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [*see Clinical Studies (14.4)*].

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-DRSS was significantly greater in both EYLEA treatment groups (2Q4 and 2Q8) when compared to the control group.

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in Table 8 below.

Table 8: Proportion of Patients who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 (LOCF[a]) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks[b]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks[b]	EYLEA 2 mg Q4 weeks	Control
Evaluable Patients[c]	N=101	N=97	N=99	N=148	N=153	N=150
Number of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)	32 (32%)	27 (28%)	7 (7%)	56 (38%)	58 (38%)	24 (16%)
Difference[d, e](%) (97.5% CI)	24%[f] (12, 36)	21%[f] (9, 33)		22%[f] (11, 33)	22%[f] (11, 33)	

[a] Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)
[b] After treatment initiation with 5 monthly injections
[c] The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline
[d] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors
[e] Difference is EYLEA minus Control group
[f] $p<0.01$ compared with Control

Results of the evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 100 were, in general, consistent with those in the overall population.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentations [*see Dosage and Administration (2.6) and (2.7)*].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-02	Vial Kit with Injection Components	one EYLEA 2 mg/0.05 mL single-dose glass vial one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert
61755-005-03	Vial Only	one EYLEA 2 mg/0.05 mL single-dose glass vial one package insert

Storage

Refrigerate EYLEA at 2°C to 8°C (36°F to 46°F). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light.

17 PATIENT COUNSELING INFORMATION

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

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

Revised Date: August 2018

An Optical Coherence Tomography-Guided, Variable Dosing Regimen with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration

ANNE E. FUNG, GEETA A. LALWANI, PHILIP J. ROSENFELD, SANDER R. DUBOVY, STEPHAN MICHELS, WILLIAM J. FEUER, CARMEN A. PULIAFITO, JANET L. DAVIS, HARRY W. FLYNN, JR, AND MARIA ESQUIABRO

• PURPOSE: To evaluate an optical coherence tomography (OCT)-guided, variable-dosing regimen with intravitreal ranibizumab for the treatment of patients with neovascular age-related macular degeneration (AMD).

• DESIGN: Open-label, prospective, single-center, nonrandomized, investigator-sponsored clinical study.

• METHODS: In this two-year study, neovascular AMD patients with subfoveal choroidal neovascularization (CNV) (n = 40) and a central retinal thickness of at least 300 μm as measured by OCT were enrolled to receive three consecutive monthly intravitreal injections of ranibizumab (0.5 mg). Thereafter, retreatment with ranibizumab was performed if one of the following changes was observed between visits: a loss of five letters in conjunction with fluid in the macula as detected by OCT, an increase in OCT central retinal thickness of at least 100 μm, new-onset classic CNV, new macular hemorrhage, or persistent macular fluid detected by OCT at least one month after the previous injection of ranibizumab.

• RESULTS: At month 12, the mean visual acuity improved by 9.3 letters ($P < .001$) and the mean OCT central retinal thickness decreased by 178 μm ($P < .001$). Visual acuity improved 15 or more letters in 35% of patients. These visual acuity and OCT outcomes were achieved with an average of 5.6 injections over 12 months. After a fluid-free macula was achieved, the mean injection-free interval was 4.5 months before another reinjection was necessary.

• CONCLUSION: This OCT-guided, variable-dosing regimen with ranibizumab resulted in visual acuity outcomes similar to the Phase III clinical studies, but required fewer intravitreal injections. OCT appears useful for determining when retreatment with ranibizumab is necessary. (Am J Ophthalmol 2007;143:566–583.

INHIBITION OF VASCULAR ENDOTHELIAL GROWTH FACtor-A (VEGF) is an effective strategy for the treatment of neovascular age-related macular degeneration (AMD).[1–4] The most effective treatment uses ranibizumab (Lucentis, Genentech Inc, South San Francisco, California, USA), a recombinant, humanized, monoclonal antibody antigen-binding fragment (Fab) that neutralizes all biologically active forms of VEGF.[5] In the two Phase III clinical studies using intravitreal injections of ranibizumab, mean visual acuity improved over 24 and 12 months, respectively.[2,3] This was the first therapy for neovascular AMD to show any improvement in mean visual acuity. In these studies, statistically significant benefits were observed for all the primary and secondary efficacy endpoints when compared with control groups. To obtain these impressive results, investigators followed a fixed-dosing regimen requiring an injection of ranibizumab, 0.5 mg or 0.3 mg, every month for two years.

The first suggestion that frequent intravitreal injections of ranibizumab could result in improved visual acuity came from the earlier Phase I/II studies.[6,7] In these studies, ranibizumab was injected every two or four weeks into eyes of patients with neovascular AMD and these patients were followed for 140 days or 210 days. The number of ranibizumab injections ranged from five to nine depending on the study and the cohort within each study. Despite differences in the overall number of injections, the outcomes from these studies were very similar. Mean visual acuity improved and these improvements were associated with an absence of angiographic leakage from choroidal neovascularization (CNV) and an absence of fluid in the macula as assessed by optical coherence tomography (OCT) (Rosenfeld PJ, unpublished data, 2003).

After completion of these Phase I/II studies, most of the study participants enrolled in an open-label extension study to evaluate the safety and tolerability of long-term (up to four years) continued treatment with intravitreal

See accompanying Editorial on page 679.
Accepted for publication Jan 13, 2007.
From the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida (G.A.L., P.J.R., S.R.D., W.J.F., C.A.P., J.L.D., H.W.F., M.E.); Pacific Eye Associates, California Pacific Medical Center, San Francisco, California (A.E.F.); University Eye Hospital Vienna, Austria (S.M.).

Inquiries to Philip J. Rosenfeld, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 N.W. 17th Street, Miami, FL 33136; e-mail: prosenfeld@med.miami.edu

0002-9394/07/$32.00
doi:10.1016/j.ajo.2007.01.028

injections of ranibizumab (Heier JS and associates. ARVO 2005, E-Abstract 1393). Although the extension study initially required monthly injections of ranibizumab after the patient was enrolled, the study was subsequently amended to permit reinjection only if needed as determined by the treating physician. As a result of retreatment being offered at the discretion of the investigator, some patients received monthly injections with ranibizumab to maintain their visual acuity, whereas others were reinjected less frequently or not at all. During this extension study at the Bascom Palmer Eye Institute, OCT imaging was used to follow many of these patients in conjunction with fluorescein angiography, and OCT appeared to detect the earliest signs of fluid reaccumulating in the macula even before leakage could be detected by fluorescein angiography (Rosenfeld PJ, unpublished data, 2003).

Based on these observations from the Phase I/II and extension studies, an investigator sponsored trial known as the Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab (Lucentis) [PrONTO] study was designed to investigate the role of OCT imaging in a variable dosing regimen with ranibizumab at the Bascom Palmer Eye Institute. This report describes the 12 month results of the PrONTO Study.

METHODS

PRONTO IS A TWO-YEAR, OPEN-LABEL, PROSPECTIVE, single-center clinical study designed to investigate the efficacy, durability, and safety of a variable dosing regimen with intravitreal ranibizumab in patients with neovascular AMD. The PrONTO Study is an investigator sponsored trial supported by Genentech, Inc, and performed with the approval of the Food and Drug Administration. Before the initiation of the study, additional approval for the PrONTO study was obtained from the Institutional Review Board at the University of Miami Miller School of Medicine. Informed consent was obtained from all patients before determination of full eligibility, and the study was performed in accordance with the Health Insurance Portability and Accountability Act (HIPAA). The PrONTO Study is registered at www.clinicaltrials.gov, and the clinical trial accession number is NCT00344227.

The major efficacy end points were the change in visual acuity and OCT measurements from baseline and the number of ranibizumab injections required over two years. Other efficacy end points included the number of consecutive monthly injections required from baseline to achieve a fluid-free macula as determined by OCT. After a fluid-free macula was achieved, the durability of the treatment effect was determined by calculating the time until the next injection was needed because of fluid reaccumulating in the macula, otherwise known as the injection-free interval. Finally, after the injections resumed, we calculated the follow-up number of reinjections required to once again achieve a fluid-free macula.

TABLE 1. Major Eligibility Criteria for Enrollment into the PrONTO Study

Inclusion criteria
Age 50 years or older.
Active primary or recurrent macular neovascularization secondary to AMD involving the central fovea in the study eye with evidence of disease progression.
OCT central retinal thickness ≥300 microns.
Best-corrected visual acuity, using ETDRS charts, of 20/40 to 20/400 (Snellen equivalent) in the study eye.
Exclusion criteria
More than three prior treatments with verteporfin photodynamic therapy.
Previous participation in a clinical trial (for either eye) involving antiangiogenic drugs (pegaptanib, ranibizumab, anecortave acetate, protein kinase C inhibitors).
Previous subfoveal focal laser photocoagulation in the study eye.
Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within one month preceding day 0.
Subfoveal fibrosis or atrophy in the study eye.
History of vitrectomy surgery in the study eye.
Aphakia or absence of the posterior capsule in the study eye.
History of idiopathic or autoimmune-associated uveitis in either eye.

AMD = age-related macular degeneration; PrONTO = Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab study; OCT = optical coherence tomography; ETDRS = Early Treatment of Diabetic Retinopathy Study.

At the start of the study, only one eye of a patient was determined to be eligible and assigned as the study eye. The major eligibility criteria are shown in Table 1. The major inclusion criteria included a diagnosis of neovascular AMD with a baseline protocol visual acuity letter score from 20 to 70 letters using the Early Treatment Diabetic Retinopathy Study chart at two meters (Snellen equivalent of 20/40 to 20/400) obtained using a standard refraction protocol[8] and an OCT 1 mm central retinal thickness of at least 300 μm. There were no exclusion criteria for preexisting cardiovascular, cerebrovascular, or peripheral vascular conditions. Of note, all fluorescein angiographic lesion types and lesion sizes were eligible for the study. The angiographic lesion types at baseline were independently assessed by three of the investigators (P.J.R., S.R.D., and G.A.L.) and agreement was reached on all interpretations. The diagnosis of retinal angiomatous proliferation (RAP) was independently assessed for each lesion using the characteristic features which included intraretinal hemorrhage, intraretinal vascular anastomoses, and the OCT appearance of a retinal pigment epithelial detachment

TABLE 2. The Number of Times Each Criterion was Used Alone or in Combination With Other Criteria to Retreat Neovascular AMD Patients With Ranibizumab After Month 2 Through Month 12

Retreatment criteria	Only one criterion observed for retreatment	Vision loss (≥5 letters) associated with fluid detected by OCT	Increase in central retinal thickness ≥100 microns	New-onset hemorrhage	New classic CNV
Vision loss (≥5 letters) associated with fluid detected by OCT	31	—	4*	5*	0
Increase in central retinal thickness ≥100 microns	12	4*	—	4*	0
New-onset hemorrhage	12	5*	4*	—	1
New classic CNV	7	0	0	1	—
Persistent fluid following last injection	30	—	—	—	—

AMD = age-related macular degeneration; OCT = optical coherence tomography; CNV = choroidal neovascularization.

Most patients fulfilled only one criterion for reinjection as listed in the second column, but some patients fulfilled two or more criteria and are listed in columns 3 to 6.

*Two of these individuals had three criteria for reinjection: vision loss (≥5 letters) associated with fluid detected by OCT, increase in central retinal thickness ≥100 microns, and new onset hemorrhage.

with overlying cystic changes in the retina. In calculating lesion areas, we assumed a standard disk diameter of 1.8 mm and a standard disk area (DA) of 2.54 mm^2. All digital fundus photography was performed using Topcon TRC-50IX retinal cameras (Topcon America Corp (TAC), Paramus, New Jersey, USA) with a 35 degree viewing angle and the images were stored using the Topcon Imagenet software (version 2.14, Windows 2000 v.5.0; Paramus, New Jersey, USA). Images were then transferred to an OIS workstation (OIS Winstation XP 10 3000 Auto Import Capture version 10.2.59; Sacramento, California, USA) where the lesion areas were measured.

OCT (Stratus OCT, Carl Zeiss Meditec, Dublin, California, USA) quantitative assessments were obtained using six diagonal fast, low density scans (low resolution, 128 A-scans per diagonal). The central 1 mm central retinal thickness measurements were obtained from the macular thickness maps calculated from the six low-resolution fast scans after it was confirmed that the two boundaries delineated as the internal limiting membrane (inner boundary) and the retinal pigment epithelium (RPE) and the Bruch membrane (outer boundary) were appropriately identified by the validated internal algorithm. If boundaries were incorrectly identified, then the scans were repeated until the boundaries were accurately identified by the algorithm. The central retinal thickness was defined as the distance between these inner and outer boundaries and did not include any fluid under the RPE. Eligible patients were required to have a 1 mm central retinal thickness of at least 300 μm. OCT qualitative assessments were performed using all six diagonal slow, high density scans (high resolution, 512 A-scans per diagonal). These high resolution diagonal scans were used to evaluate whether fluid was present in the macula and whether retreatment was needed. For the purposes of this study, fluid in the macula was identified as intraretinal fluid (cysts) and subretinal fluid, and a fluid-free macula was defined by the absence of retinal cysts and subretinal fluid as determined by OCT. Fluid under the RPE, otherwise known as a pigment epithelial detachment (PED), was recorded as an OCT finding in the macula but not included in any of the retreatment criteria. The decision not to include a PED in the retreatment criteria was based on prior anecdotal observations from the Phase I/II extension study with ranibizumab. In the extension study, there appeared to be little correlation between the presence of a PED and visual acuity. In addition, PEDs could remain stable for months and resolution of fluid within the PED was thought to be a lagging indicator of VEGF activity. In contrast, macular cysts and subretinal fluid appeared to respond more rapidly to the presence or absence of VEGF.

During the screening process, patients underwent a complete physical exam with laboratory testing. Laboratory testing consisted of an electrocardiogram, complete blood count, and chemistry panel performed at baseline and at month 12. Blood pressure measurements were performed at every visit. Eligible patients underwent visual acuity testing and ophthalmoscopic examinations at baseline, day 14, day 30, day 45, day 60, and monthly thereafter. Fundus photography and OCT imaging were performed at baseline and on days one, two, four, seven, 14, and 30 after the first two monthly injections, and monthly thereafter. Fluorescein angiography was performed at baseline, month 1, month 2, month 3, and every three months thereafter. All ophthalmic photographers and OCT technicians involved in the study were previously certified to participate in Food and Drug Adminstration–approved clinical trials at the Bascom Palmer Eye Institute.

After determination of eligibility, patients received an intravitreal injection of ranibizumab (LUCENTIS, Genentech, Inc) using a standard protocol at the Bascom Palmer Eye Institute. The eye was topically anesthetized with sterile 4% lidocaine and a povidone-iodine (10%) scrub was performed on the lids and lashes. A sterile speculum was placed between the lids, and povidone-

TABLE 3. Visual Acuity of Eyes With Neovascular AMD Treated With a Variable-Dosing Regimen of Ranibizumab Through 12 Months

Patients' study eyes (n = 40)	Baseline visual acuity letters (Snellen equivalent)	Day 14 visual acuity letters (Snellen equivalent)	Month 1 visual acuity letters (Snellen equivalent)	Month 3 visual acuity letters (Snellen equivalent)	Month 12 visual acuity letters (Snellen equivalent)	Change in visual acuity letter scores from baseline to month 12 visual acuity letters (Snellen equivalent)
Mean (*P* value)*	56.2	63.1	63.9	67.0	65.5	+9.3
	$20/80^{+1}$	$20/50^{-2}$ ($P < .001$)	$20/50^{-1}$ ($P < .001$)	$20/50^{+2}$ ($P < .001$)	20/50 ($P < .001$)	
Median (*P* value)†	57	65.0	66.0	71.0	68	+11.0
	$20/80^{+2}$	(20/50) ($P < .001$)	$20/50^{+1}$ ($P < .001$)	$20/40^{+1}$ ($P < .001$)	$20/40^{-2}$ ($P < .001$)	

AMD = age-related macular degeneration.
*Paired the Student *t* test.
†Paired the Wilcoxon signed-rank test.

TABLE 4. OCT Central Retinal Thickness of Eyes With Neovascular AMD Treated With a Variable-Dosing Regimen of Ranibizumab Through 12 Months

Patients' study eyes (n = 40)	Baseline central retinal thickness (μm)	Day 1 central retinal thickness (μm)	Month 1 central retinal thickness (μm)	Month 3 central retinal thickness (μm)	Month 12 central retinal thickness (μm)	Change in central retinal thickness (μM) from baseline to month 12
Mean (*P* value)*	393.9	347.1 ($P < .001$)	237.2 ($P < .001$)	204.3 ($P < .001$)	216.1 ($P < .001$)	−177.8
Median (*P* value)†	384.5	336.0 ($P < .001$)	203.5 ($P < .001$)	186.0 ($P < .001$)	199.0 ($P < .001$)	−185.5

OCT = optical coherence tomography; AMD = age-related macular degeneration.
*Paired the Student *t* test.
†Paired the Wilcoxon signed-rank test.

TABLE 5. Distribution of OCT Lesion Characteristics From Baseline Through Month 3 in Neovascular AMD Patients Treated With Ranibizumab at Day 0, Month 1, and Month 2

OCT lesion characteristics (n = 40)	Day 0 n (%)	Day 7 n (%)	Day 14 n (%)	Month 1 n (%)	Month 2 n (%)	Month 3 n (%)
Retinal cysts	36 (90%)	7 (17.5%)	6 (15%)	6 (15%)	3 (7.5%)	3* (7.5%)
Subretinal fluid	30 (75%)	19 (47.5%)	15 (37.5%)	9 (22.5%)	3 (7.5%)	1* (2.5%)
RPE detachment	29 (72.5%)	27 (67.5%)	24 (60%)	23 (57.5%)	18 (45%)	15 (37.5%)
Epiretinal membrane	9 (22.5%)	9 (22.5%)	9 (22.5%)	9 (22.5%)	9 (22.5%)	9 (22.5%)
RPE tear	0	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)

OCT = optical coherence tomography; RPE = retinal pigment epithelium; AMD = age-related macular degeneration.
*One eye had both residual retinal cysts and subretinal fluid.

iodine (5%) drops were applied over the ocular surface three times over several minutes. Additional topical anesthesia was achieved by applying a sterile cotton swab soaked in sterile 4% lidocaine to the area designated for injection in the inferotemporal quadrant. Ranibizumab (0.05 ml, 0.5 mg) in a tuberculin syringe with a 30-gauge needle was injected through the pars plana into the vitreous cavity through the sclera 3 to 4 mm posterior to the limbus. Post-injection light perception was assessed and the intraocular pressure was monitored until it was lower than 30 mm Hg. The patient was instructed to apply moxifloxacin antibiotic drops (vigamox 0.5% solution) to the study eye four times per day for three days. All patients received a call within 24 hours to assess their status and remind them to use their antibiotic drops.

Intravitreal injections of ranibizumab were administered to all patients at baseline, month 1, and month 2. Additional reinjections were given if any of the following changes were observed by the evaluating physician as shown in Table 2: (1) visual acuity loss of at least five letters with OCT evidence of fluid in the macula, (2) an increase in OCT central retinal thickness of at least 100

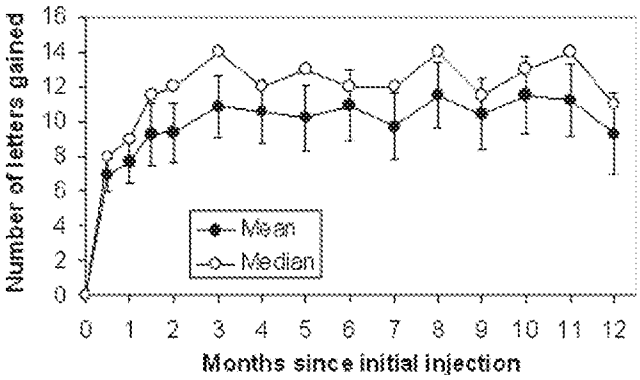


FIGURE 1. Mean and median change in visual acuity through 12 months of eyes with neovascular age-related macular degeneration (AMD) treated with a variable dosing intravitreal ranibizumab regimen. Vertical lines are 1 standard error of the means.

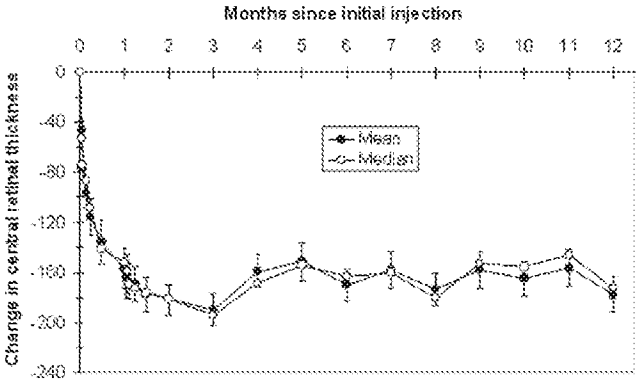


FIGURE 2. Mean and median change in the optical coherence tomography (OCT) central retinal thickness through 12 months of eyes with neovascular age-related macular degeneration (AMD) treated with a variable dosing intravitreal ranibizumab regimen. Vertical lines are 1 standard error of the means.

TABLE 6. Distribution of Visual Acuity Changes in Eyes With Neovascular AMD After 3 Doses of Ranibizumab at Month 3 and After a Variable-Dosing Regimen From Months 3 Through 12

Change in visual acuity from baseline through 12 months	Month 3 40 eyes n (%)	Month 12 40 eyes n (%)
≥6 line increase	2 (5%)	3 (7.5%)
≥3 line to <6 line increase	11 (27.5%)	11 (27.5%)
≥1 line to <3 line increase	20 (50%)	16 (40%)
No change	5 (12.5%)	5 (12.5%)
≥1 line to <3 line decrease	1 (2.5%)	3 (7.5%)
≥3 line decrease	1 (2.5%)	2 (5%)

AMD = age-related macular degeneration.

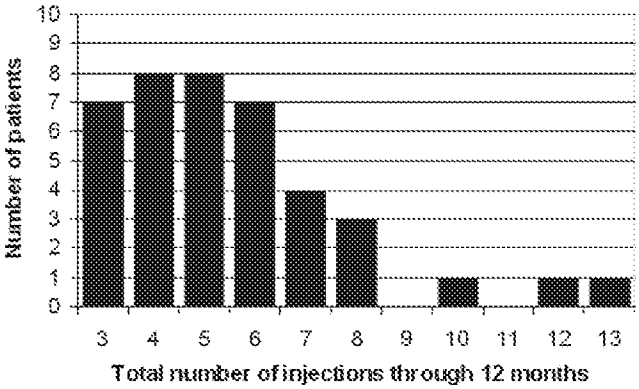
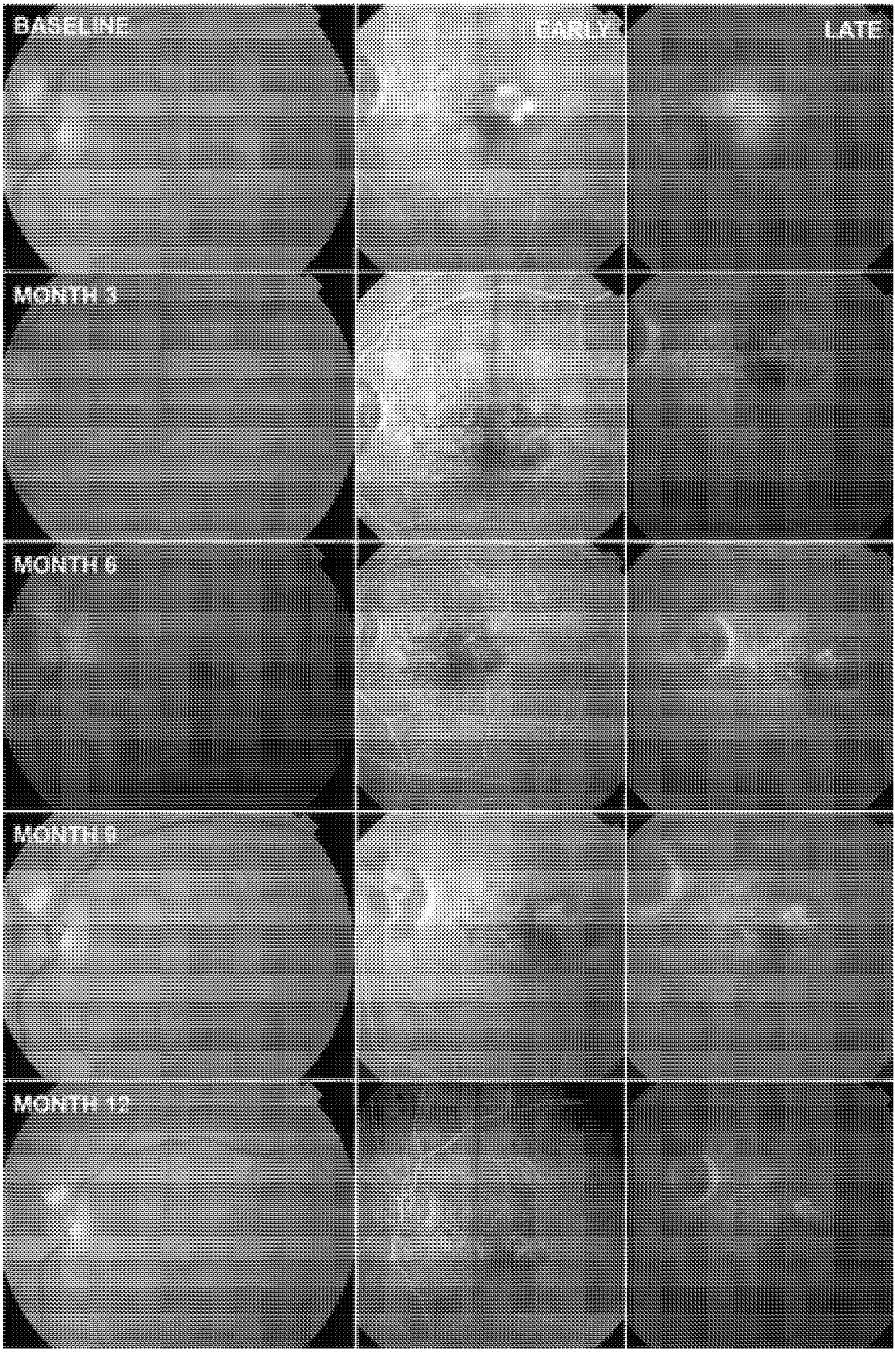


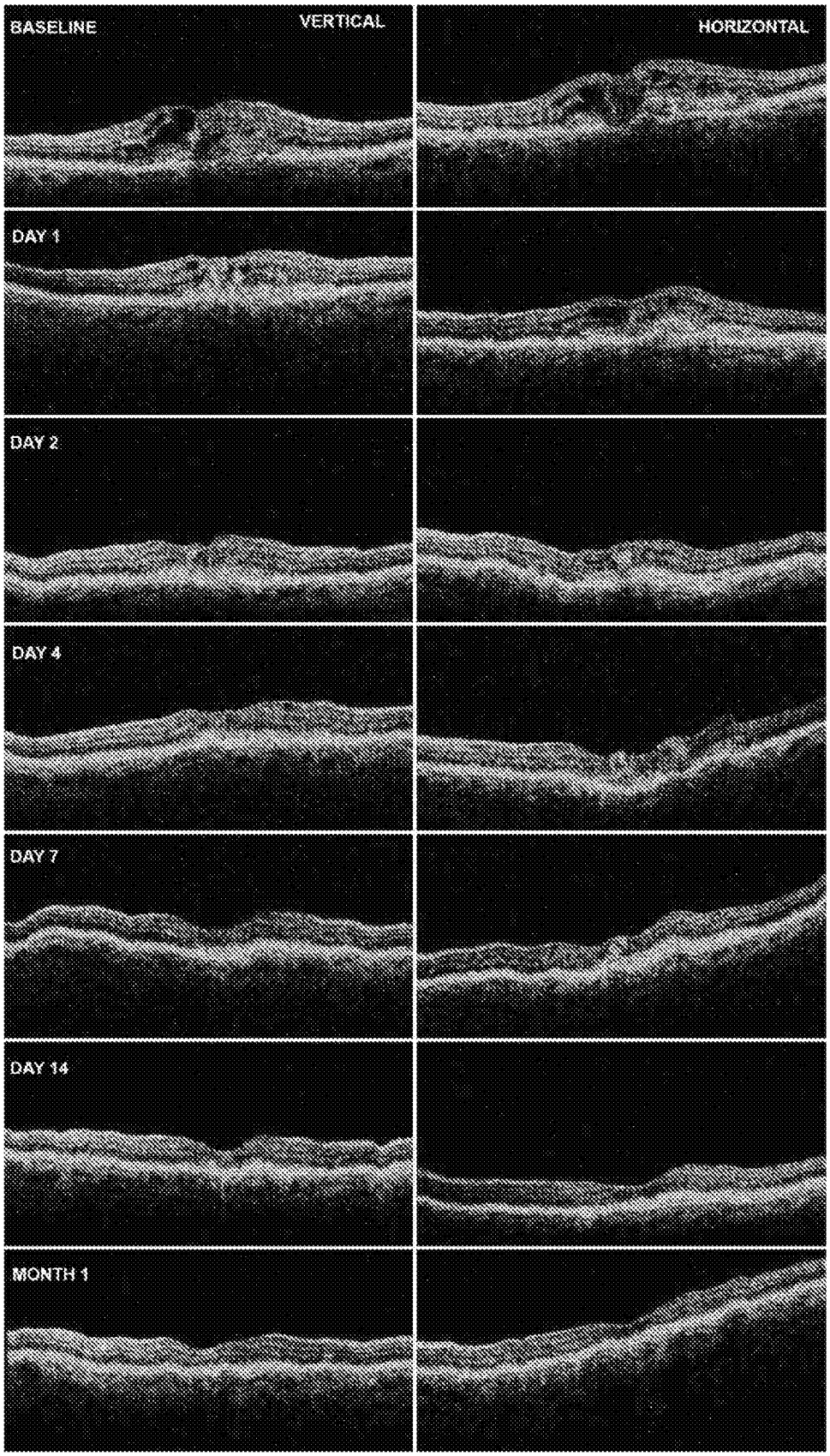
FIGURE 3. Distribution of the total number of injections of ranibizumab administered per neovascular age-related macular degeneration (AMD) patient through 12 months according to the Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab (PrONTO) study criteria.

μm, (3) new macular hemorrhage, (4) new area of classic CNV, or (5) evidence of persistent fluid on OCT at least one month after the previous injection. All criteria were based on comparisons with the previously scheduled visit. If a reinjection was performed as part of an unscheduled visit, then the patient returned at the next scheduled visit for follow-up, but all subsequent reinjection decisions were postponed until the next scheduled visit at least one month after the injection. If any single criterion for reinjection was fulfilled, then the intravitreal injection was performed as previously described.

The major outcome measurements in the PrONTO study included Early Treatment Diabetic Retinopathy Study visual acuity letter scores, OCT central retinal thickness measurements, the change in visual acuity letter scores and OCT measurements from baseline, the consecutive number of injections required to achieve a fluid-free macula from baseline, the injection-free interval after a fluid-free macula was achieved, the number of consecutive reinjections required to achieve a fluid-free macula after the fluid started to reaccumulate and injections were

FIGURE 4. Case 1: A 100-year-old woman with neovascular age-related macular degeneration (AMD) diagnosed with predominantly classic choroidal neovascularization (CNV) in her left eye, given three ranibizumab injections, and then followed through month 12. Color fundus images with early and late phase fluorescein angiographic images are shown at baseline, at month 3 (one month after the third injection), and then at month 6, month 9, and month 12 without any additional injections of ranibizumab. At months 6 and 12, fundus photography was performed using a 50 degree viewing angle rather than the protocol 35 degree angle.





resumed, and the total number of injections received by a patient during one year.

For the mean visual acuity letter scores and central retinal thickness measurements during the first 12 months, the data were statistically compared with mean baseline values using the paired Student *t* test. Median measurements were compared with median baseline values using the paired Wilcoxon signed-rank test. The influence of baseline fluorescein angiographic lesion types on the number of injections over 12 months was assessed using one-way analysis of variance and the Kruskal-Wallis test. The influence of baseline acuity and lesion size in disk areas on the number of injections and the influence of the number of injections on visual acuity outcomes were assessed using the Pearson correlation analysis and Spearman nonparametric correlation analysis. Statistical significance was defined as $P < .05$.

RESULTS

• BASELINE CHARACTERISTICS: Between August 2004 and April 2005, 69 patients were screened for the study and 40 patients were enrolled. Twenty-nine patients were excluded from the study for the following reasons: OCT central retinal thickness less than 300 μm (nine patients), declined participation in the study after screening because of the rigorous follow-up schedule (seven patients), visual acuity either better than 20/40 or worse than 20/400 (four patients), inability to obtain reproducible OCT central retinal thickness measurements because of unreliable boundary detection (three patients), localized retinal detachment (two patients), previous enrollment in a clinical trial involving anti-angiogenic drugs (two patients), RPE tear (one patient), and no evidence of macular neovascularization (one patient). Of the 40 patients enrolled in the study, the mean age was 83.5 years (standard deviation [SD] =7.2) and the median age was 83 years (range, 69 to 100 years), 26 were women (65%), and all the participants were white. Fifteen eyes (37.5%) were phakic and 25 eyes (62.5%) were pseudophakic. Fourteen of the 40 eyes had undergone some prior treatment for neovascular AMD including intravitreal pegaptanib (four eyes), photodynamic therapy (PDT) alone (three eyes), PDT with intravitreal triamcinolone acetonide (five eyes), PDT followed by intravitreal pegaptanib (one eye), and laser photocoagulation (one eye).

At baseline, the mean and median visual acuity letter scores were 56 ($20/80^{+1}$) and 57 ($20/80^{+2}$), respectively (Table 3). Baseline mean and median OCT 1 mm central retinal thickness measurements were 394 μm and 385 μm, respectively (Table 4). The OCT findings at baseline included retinal cysts (36 eyes; 90%), subretinal fluid (30 eyes; 75%), PED (29 eyes; 72.5%), and epiretinal membrane (nine eyes, 22.5%; Table 5). At baseline, the neovascular lesions were categorized by fluorescein angiography as occult with no classic lesions (10 eyes; 25%), minimally classic lesions (23 eyes; 57.5%), and predominantly classic lesions (seven eyes; 17.5%). Overall, 10 of the 40 lesions (25%) were categorized as RAP lesions. The mean and median baseline lesion areas were 3.5 DAs (SD = 2.4) and 2.8 DAs (range, 0.6 to 10), respectively. The baseline mean systolic/diastolic blood pressure was 149/78.

• VISUAL ACUITY AND OCT OUTCOMES AT THREE MONTHS: After the first injection of ranibizumab at baseline, an improvement in visual acuity was detected by day 14, the first follow-up visit when visual acuity was measured after the first injection (Table 3; Figure 1). The mean and median visual acuity scores improved by 6.9 letters ($P < .001$) and 7.5 letters ($P < .001$), respectively. During the first three months, visual acuity continued to improve. By month three, one month after the third injection, there was a mean and median visual acuity increase of 10.8 letters ($P < .001$) and 10.5 letters ($P < .001$), respectively. At month three, 13 eyes (32.5%) gained at least 3 lines of visual acuity, with two eyes (5%) gaining at least 6 lines compared with baseline. One eye lost more than 3 lines of visual acuity by three months because a tear of the RPE developed within seven days after the first injection (Tables 5 and 6).

The improvement in visual acuity was associated with a decrease in central retinal thickness (Table 4, Figure 2). One day after the first injection of ranibizumab, a statistically significant decrease in the central retinal thickness was detected with the mean and median thickness measurements decreasing by 47 μm ($P < .001$) and 48.5 μm ($P < .001$), respectively. The central retinal thickness continued to decrease over the next three months. By month three, the mean and median central retinal thickness measurements had decreased by 189.7 μm ($P < .001$) and 198.5 μm ($P < .001$), respectively.

The correlations between the decrease in OCT central retinal thickness and the improvement in visual acuity were explored using both Pearson correlation and Spearman nonparametric correlation analyses. At one month, there were no statistically significant correlations between the decrease in central retinal thickness and the improve-

FIGURE 5. Case 1: Optical coherence tomography (OCT) response to the first ranibizumab injection from baseline through month 1 in an eye with neovascular age-related macular degeneration (AMD) and predominantly classic choroidal neovascularization (CNV). Vertical (left side) and horizontal (right side) OCT scans and central retinal thickness measurements of her left eye are shown at baseline (406 μm; visual acuity [VA]: 20/80), ranibizumab no. 1 injected; day 1 (327 μm); day 2 (307 μm); day 4 (281 μm); day 7 (225 μm); day 14 (219 μm; VA: 20/50); month 1 (183 μm; VA: 20/50), ranibizumab no. 2 injected.

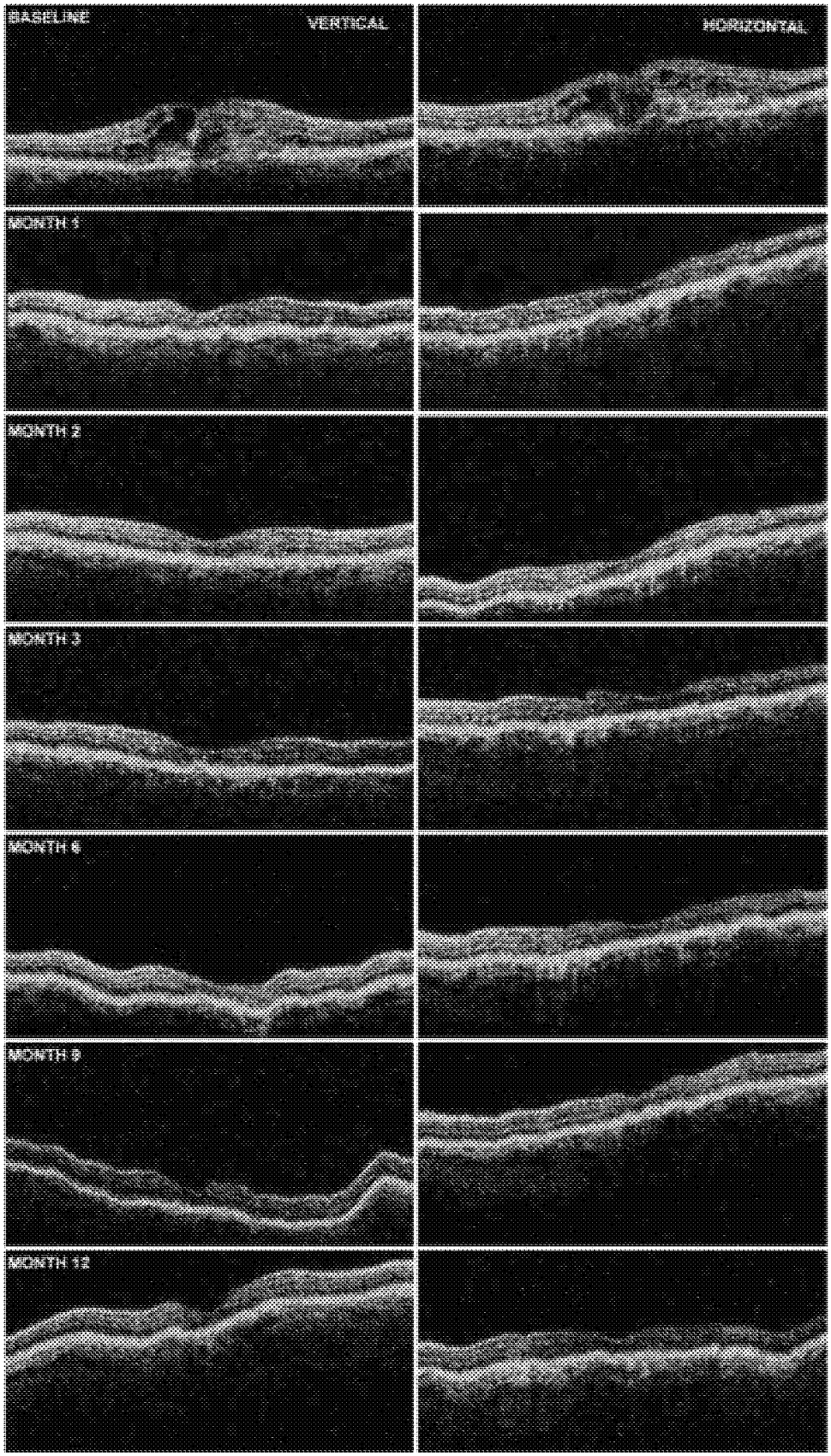


TABLE 7. Number of Reinjections With Ranibizumab Performed per Month in Eyes With Neovascular AMD Using the Variable-Dosing Regimen From Months 3 Through 12

Follow-up visit	Number (%) receiving the first reinjection after month 2 (n = 33)	Total number (%) reinjected at monthly follow-up visits(n = 33)
Month 3	3 (7.5)	3 (7.5)
Month 4	6 (15.0)	9 (22.5)
Month 5	10 (25.0)	14 (35.0)
Month 6	3 (7.5)	7 (17.5)
Month 7	3 (7.5)	11 (27.5)
Month 8	0	6 (15.0)
Month 9	2 (5.0)	14 (35.0)
Month 10	1 (2.5)	6 (15.0)
Month 11	2 (5.0)	13 (32.5)
Month 12	3 (7.5)	19 (47.5)

AMD = age-related macular degeneration.

ment in visual acuity (Pearson, $r = .25$, $P = .12$; Spearman, $r = .23$, $P = .15$). However, there were significant correlations between the decrease in central retinal thickness at one month and the subsequent improvement in visual acuity seen at two months (Pearson, $r = .57$, $P < .001$; Spearman, $r = .47$, $P = .002$) and three months (Pearson, $r = .51$, $P = .001$; Spearman, $r = .36$, $P = .021$). In addition, significant correlations were identified between the change in thickness at two months and the visual acuity changes at two months (Pearson, $r = .36$, $P = .023$; Spearman, $r = .41$, $P = .009$) and three months (Pearson, $r = .31$, $P = .05$; Spearman, $r = .38$, $P = .017$). Finally, significant correlations were observed between the decrease in retinal thickness and the improvement in visual acuity at three months (Pearson, $r = .36$, $P = .024$; Spearman, $r = .34$, $P = .034$).

The PrONTO OCT definition of fluid in the macula included retinal cysts and subretinal fluid, but not sub-RPE fluid, otherwise known as a PED. Of the 36 eyes with cystic changes in the retina at baseline, 30 eyes showed complete resolution of the retinal cysts by day 7 (Table 5). By one month after the injection, only six eyes were found to contain retinal cysts, with three eyes containing retinal cysts at month 2 and month 3. Of the 30 eyes with subretinal fluid at baseline as detected by OCT, 19 eyes continued to have subretinal fluid at day 7 after the first injection, nine eyes continued to have subretinal fluid at month 1, three eyes at month 2, and only one eye at month 3. At the month 3 visit, only three eyes required an injection of ranibizumab because of persistent fluid in the macula; two eyes with residual retinal cysts and one eye with both residual cysts and subretinal fluid (Table 5).

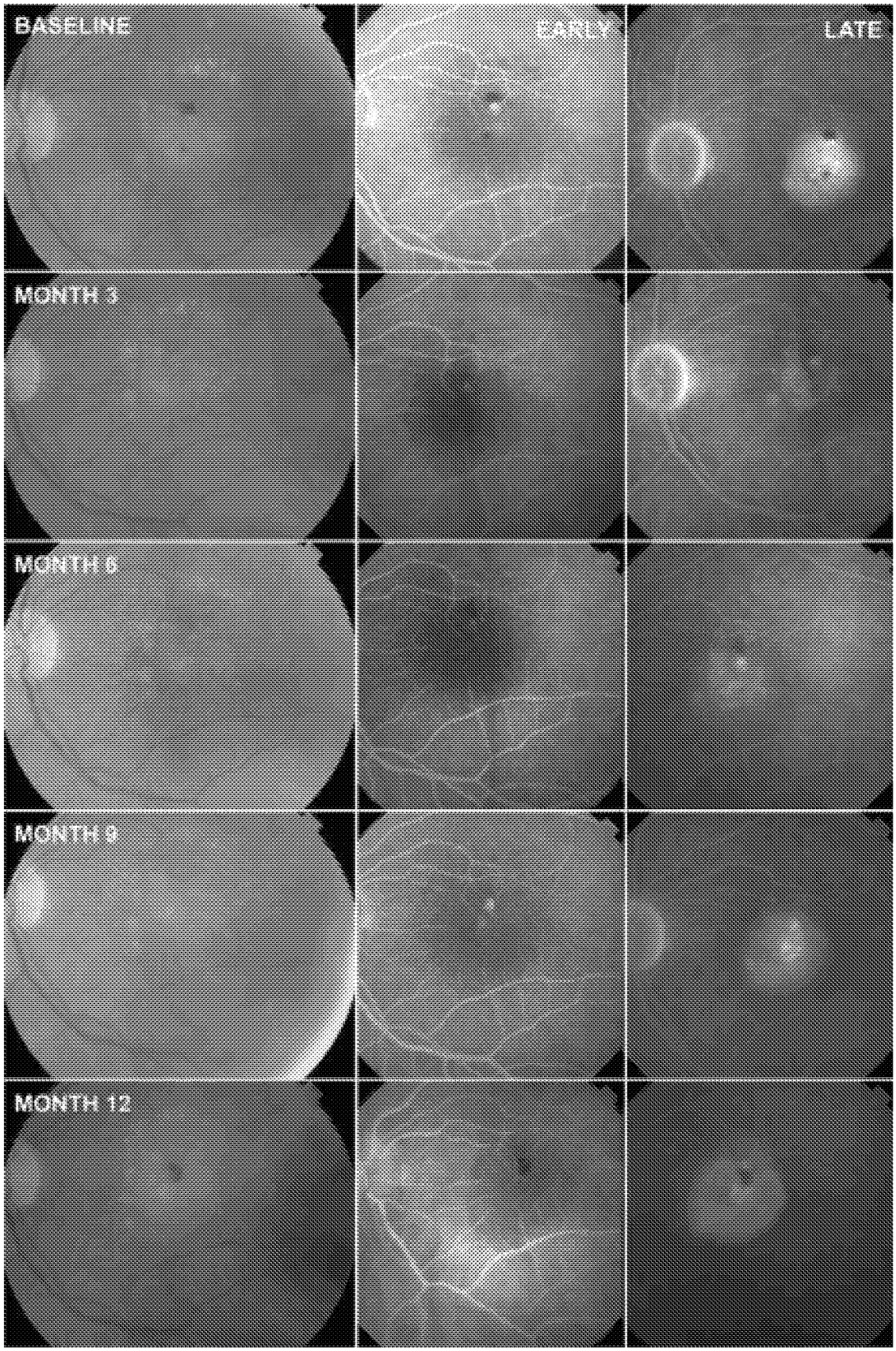
Fluid contained within a PED appeared to take longer to resolve compared with intraretinal cysts and subretinal fluid (Table 5). Of the 29 eyes with evidence of a PED at baseline, only 14 eyes showed resolution of the PED by month 3 with the remaining 15 eyes showing at least some decrease in the amount of fluid within the PED. One of the eyes with a PED at baseline was the same eye that developed a tear of the RPE within seven days after the first injection.

At the month 3 visit, 37 of the 40 eyes did not receive an injection. Of the three eyes that did receive an injection, two had persistent intraretinal cysts and one had both persistent cysts and subretinal fluid (Table 5). A fluid-free macula was eventually achieved in two of the eyes, with one eye requiring two more consecutive monthly injections and the other eye requiring three more consecutive monthly injections. One eye never became fluid-free during the first year of the study and required 13 injections through month 12.

• RETREATMENT WITH RANIBIZUMAB FROM MONTH 3 TO MONTH 12: At month 12, 100% of patients returned for follow-up. Of the 880 study visits scheduled during the first 12 months, only eight scheduled study visits were missed by different patients at different times resulting in an overall study compliance of 99.1%. A total of 11 unscheduled visits occurred primarily because of patients reporting a worsening of their visual acuity, and four of these visits resulted in a reinjection based on the retreatment criteria. All patients evaluated at an unscheduled visit returned for their next regularly scheduled visit.

After the month 2 visit, only one of the reinjection criteria needed to be fulfilled; however, at any given visit, several criteria could be fulfilled (Table 2). A total of 102 reinjections were performed beginning at month 3 through month 12 based on our retreatment criteria. The most common reason for reinjection was the loss of at least five letters of visual acuity in association with macular fluid detected by OCT. Two of the criteria did not require any OCT imaging, and these criteria were the presence of a new hemorrhage and the appearance of new classic CNV. Twenty of the 102 reinjections were performed because of

FIGURE 6. Case 1: Optical coherence tomography (OCT) response from baseline through month 12 in an eye with neovascular age-related macular degeneration (AMD) and predominantly classic choroidal neovascularization (CNV) given a total of three injections through month 2 with no additional injections performed through month 12. Vertical (left side) and horizontal (right side) OCT scans and central retinal thickness measurements are shown of her left eye at baseline (406 μm; visual acuity [VA]: 20/80), ranibizumab no. 1 injected; month 1 (183 μm; VA: 20/50), ranibizumab no. 2 injected; month 2 (180 μm; VA: 20/50), ranibizumab no. 3 injected; month 3 (184μm; VA: 20/32), observed; month 6 (179 μm; VA: 20/50), observed; month 9 (203 μm; VA: 20/50), observed; month 12 (180 μm; VA: 20/40), observed.



new hemorrhage or new classic CNV alone or in combination. Even though both of these retreatment criteria did not rely on OCT imaging, investigators did observe either an increase in intraretinal cysts or subretinal fluid at these visits, which are qualitative OCT changes consistent with the appearance of recurrent fluid. However, the increase in the OCT central retinal thickness measurements at these visits were less than the 100 μm increases required to trigger a retreatment.

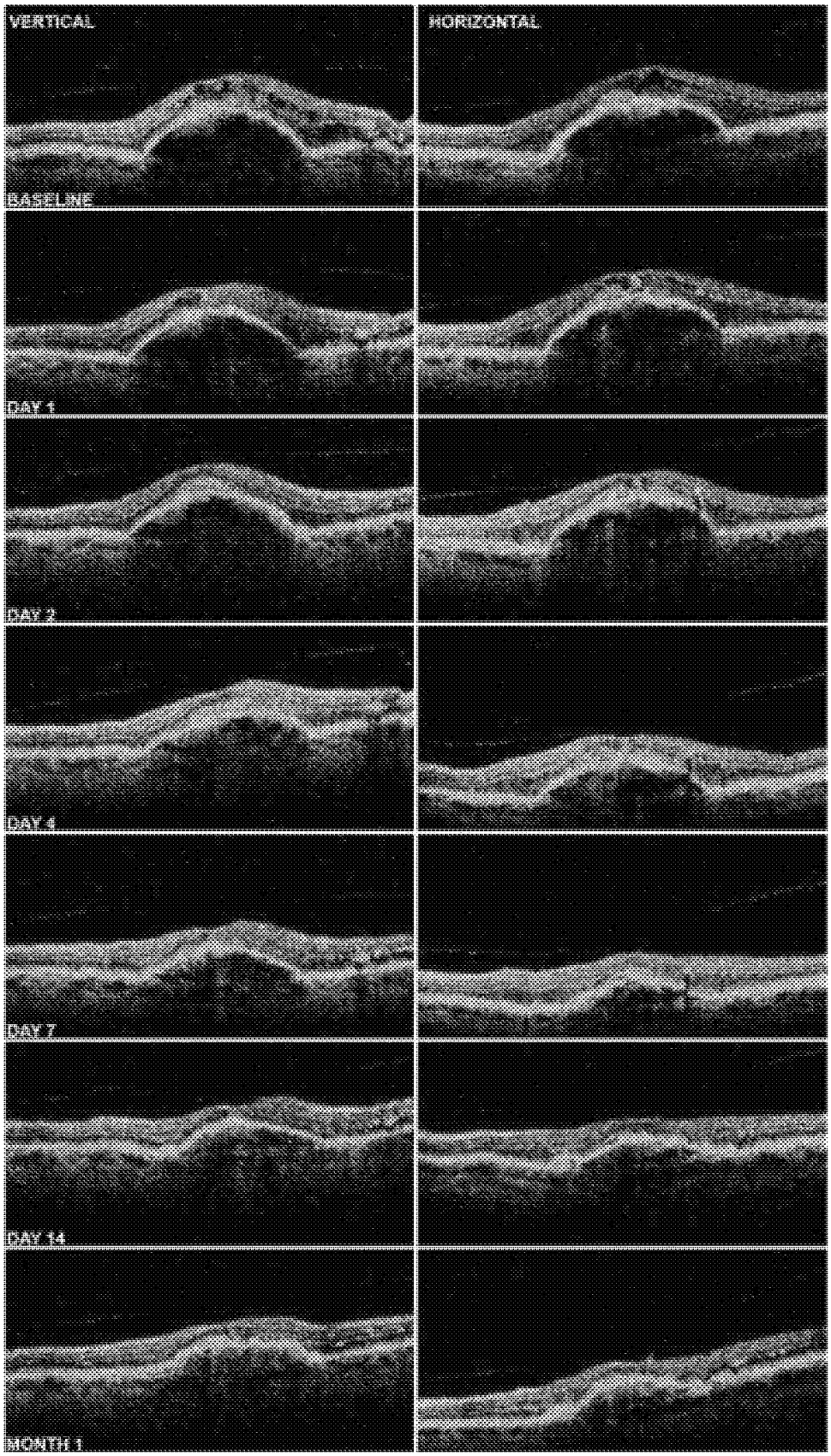
The mean and median number of injections for the first year were 5.6 (SD 2.3) and 5.0 (range, three to 13), respectively, of a possible 13 injections from day 0 through month 12. Three of these injections were mandated by the protocol and given during the first three months. After the first three injections, seven patients never needed another injection (Figure 3). Figures 4, 5, and 6 show the images of an eye with a predominantly classic lesion that required a total of only three injections over 12 months. In contrast to the seven eyes that received just the three injections over 12 months, one eye never became fluid-free and received a total of 13 injections. Of the 39 eyes that eventually achieved a fluid-free macula, the mean and median number of monthly consecutive injections from baseline that were required to achieve a fluid-free macula were 1.5 (SD 1.1) and 1.0 (range, one to six), respectively.

Thus a total of 39 eyes eventually became fluid-free; 37 of these eyes eventually developed some recurrent fluid during the first year. Of the 37 eyes that developed some recurrent fluid, 32 received a retreatment during the first 12 months. Of the 39 eyes that became fluid-free, seven never needed another injection after the last scheduled injection at month 2. Therefore, five of the 37 eyes that developed some recurrent fluid did not meet any of the criteria for retreatment during the first year. For the 32 eyes that did develop recurrent fluid and were reinjected after month 2, the mean and median duration of the injection-free interval was 4.5 months (SD 2.7) and 3.0 months (range, two to 10 months), respectively. After achieving a fluid-free status following the last scheduled injection at month 2, Table 7 shows the monthly visit when eyes received their first reinjection based on the criteria in Table 2. Table 7 also shows the total number of eyes requiring any injection at each monthly visit. Of the 32 eyes that were reinjected, 27 eyes returned to a fluid-free state before month 12. The mean and median number of consecutive monthly reinjections required until the macula was once again fluid-free was 1.2 (SD 0.6) and one (range, one to four), respectively. Figures 7 to 10 show the images of an eye with a RAP lesion that required a total of seven injections with injection-free intervals ranging from two to three months.

• VISUAL ACUITY AND OCT OUTCOMES AT 12 MONTHS: At 12 months, the mean and median visual acuity scores improved compared with baseline by 9.3 letters ($P < .001$) and 11 letters ($P < .001$), respectively (Table 3; Figure 1). Fourteen eyes (35%) gained at least 3 lines of vision with three eyes (7.5%) gaining at least 6 lines of vision (Table 6). Thirty-three eyes (82.5%) avoided any loss of letters with 38 eyes (95%) avoiding a loss of at least three lines (15 letters) of visual acuity by 12 months. The overall improvement in visual acuity was associated with a decrease in central retinal thickness. The mean and median thickness measurements decreased by 177.8 μm ($P < .001$) and 185.5 μm ($P < .001$), respectively (Table 4; Figure 2). The correlations between the improvement in visual acuity and decrease in OCT central retinal thickness measurements at 12 months were found to be significant for the Pearson analysis, but borderline for the Spearman analysis (Pearson, $r = .38$, $P = .016$; Spearman, $r = .31$, $P = .051$). However, both analyses showed significance when the change in OCT central retinal thickness at one month was correlated with the eventual change in visual acuity at 12 months (Pearson, $r = .37$, $P = .019$; Spearman, $r = .38$, $P = .015$). These results suggest that the initial decrease in OCT measurements are predictive of future visual acuity improvements, whereas the subsequent OCT measurements that can fluctuate as part of a variable dosing regimen are less reliable predictors of visual acuity at any given month.

Retreatment was guided primarily by the presence of fluid in the macula as defined by intraretinal cysts and subretinal fluid which were also the major contributors to the overall central retinal thickness measurement, and a positive correlation was found between the central retinal thickness measurements and visual acuity outcomes. However, retreatment decisions were not guided by the presence or absence of a PED. One way to assess whether the existence of a PED was a variable that influenced visual acuity outcomes would be to analyze whether the presence or absence of a PED at baseline and after the first three consecutive monthly injections were associated with visual acuity outcomes at 12 months. Using the Student t test and the Mann-Whitney U nonparametric test, we found no association between a PED at baseline with visual

FIGURE 7. Case 2: A 82-year-old woman with neovascular age-related macular degeneration (AMD) and a history of three prior photodynamic therapy treatments to her left eye subsequently diagnosed with retinal angiomatous proliferation that appeared as occult with no classic choroidal neovascularization (CNV) by fluorescein angiography and received seven intravitreal injections of ranibizumab over 12 months. Color fundus images with early- and late-phase fluorescein angiographic images are shown at baseline, month 3 (1 month after the third injection), month 6, month 9, and month 12. Four additional ranibizumab injections were given at month 5, month 7, month 9, and month 12.



acuity at 12 months ($P = .78$; $P = .57$) or a PED at three months with visual acuity at 12 months ($P = .79$; $P = .68$).

There was no statistically significant correlation between the need for retreatment over 12 months and baseline visual acuity or baseline lesion size. The influence of baseline acuity and lesion size in disk areas on the number of reinjections was assessed with both Pearson correlation and Spearman nonparametric correlation analyses. No correlation was found between number of reinjections and baseline acuity (Pearson, $r = -.03$, $P = .88$; Spearman, $r = .14$, $P = .39$) or lesion size and (Pearson, $r = -.06$, $P = .71$; Spearman $r = -.04$, $P = .83$).

When the major baseline angiographic lesion types were analyzed over 12 months, they all required about the same number of injections. Overall, occult with no classic lesions (n = 10) received 5.4 injections (SD 2.2), minimally classic lesions (n = 23) received 5.6 injections (SD 2.1), and predominantly classic lesions (n = 7) received 5.7 injections (SD 3.4). A one-way parametric analysis of variance showed no statistically significant difference between these lesion types with respect to the number of injections performed ($P = .96$). However, there was statistical significance when comparing RAP lesions (n = 10) with non-RAP lesions (n = 30) ($P = .013$). RAP lesions received 7.1 injections (SD 2.2), whereas non-RAP lesions received 5.0 injections (SD 2.2). Similarly, when a one-way nonparametric analysis was performed (the Kruskal-Wallis test), no statistically significant difference was found between occult with no classic, minimally classic, or predominantly classic lesions with respect to the number of injections performed ($P = .89$); however, a significant difference was found when comparing RAP lesions with non-RAP lesions ($P = .003$).

The influence of reinjections on the change in visual acuity letter scores at 12 months was assessed with both Pearson and Spearman correlation analyses. Although no statistically significant correlation was found with either analysis (Pearson, $r = -.25$, $P = .13$; Spearman, $r = -.31$, $P = .054$), the results suggest a trend towards a possible correlation between more frequent injections and worse visual acuity outcome.

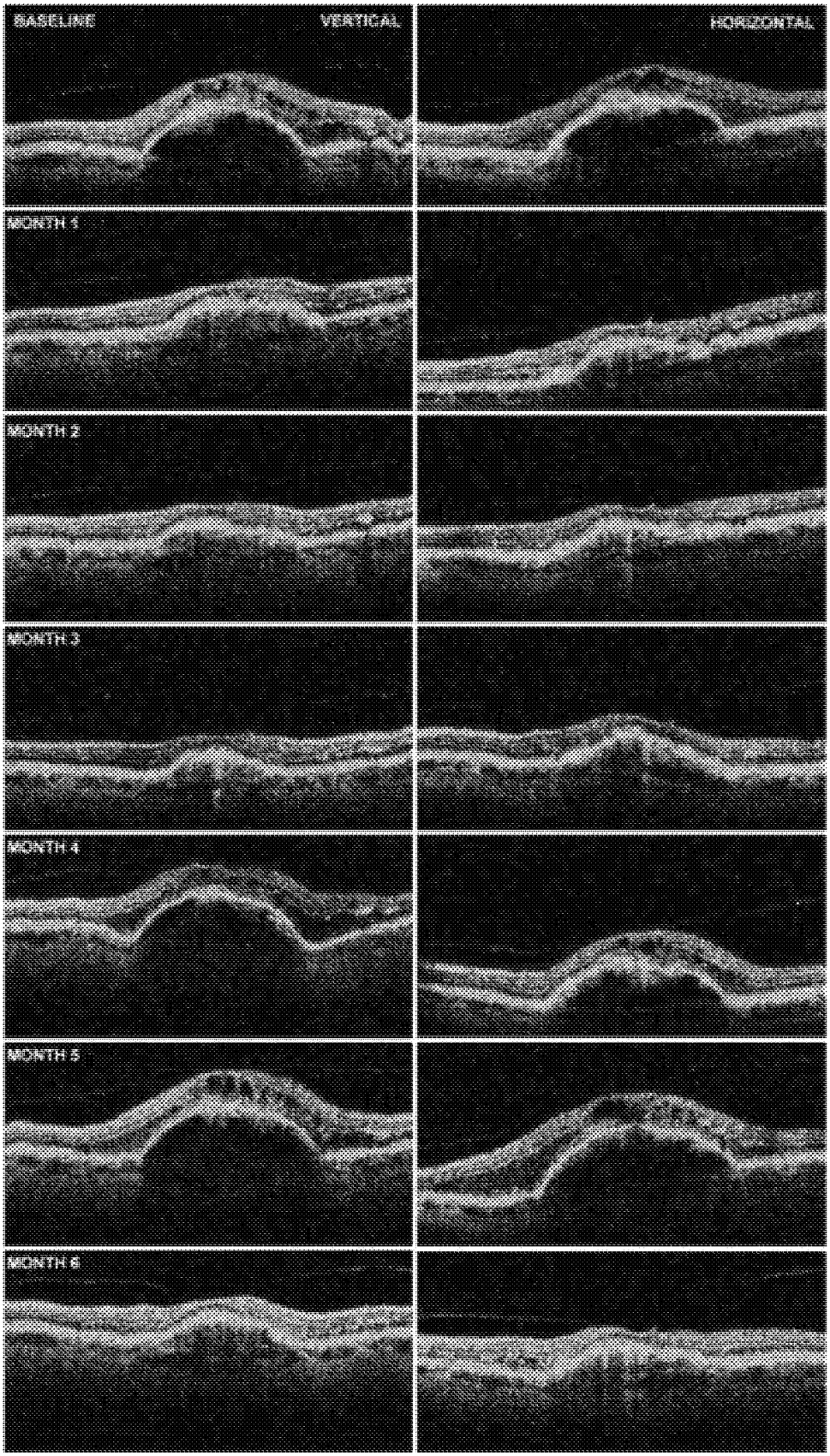
• **SAFETY:** There were no ocular or systemic adverse events attributable to the injection of ranibizumab. A total of 222 injections were performed and there were no episodes of endophthalmitis, uveitis, retinal detachment, retinal tear, vitreous hemorrhage, lens damage, cataract progression, or prolonged intraocular pressure elevation. No systemic thromboembolic events occurred and there were no deaths. No hypertension was newly diagnosed during the study. There was no cataract progression noted on clinical exam and no cataract surgery was performed. After one year, there was a mean change in systolic blood pressure of −8 mm Hg and a mean change in diastolic blood pressure of −5 mm Hg.

DISCUSSION

IN THE PRONTO STUDY, INTRAVITREAL INJECTIONS OF ranibizumab were shown to rapidly reduce the amount of macular fluid in eyes of patients with neovascular AMD while improving visual acuity. Within one day, both the mean and median OCT central retinal thickness measurements decreased significantly, and by day 14, both the mean and median visual acuity measurements had improved. Continued improvements were evident within the first 3 months after the three scheduled ranibizumab injections and these improvements were maintained through 12 months using a variable dosing regimen. After month 2, injections were stopped if the macula was found to be fluid-free and injections were resumed after certain retreatment criteria were met. When injections resumed, a single injection was usually sufficient to restore a fluid-free macula.

The PrONTO study visual acuity outcomes were similar to the results from the 0.5 mg treatment groups in the two Phase III clinical trials with ranibizumab that used a fixed monthly dosing regimen.[2,3] These two Phase III trials are known by the acronyms MARINA and ANCHOR. In the MARINA trial, mean visual acuity improved by 7.2 letters and in the ANCHOR trial, mean visual acuity improved 11.3 letters. In the PrONTO study, visual acuity improved by 9.3 letters at 12 months. Although patients in the MARINA and ANCHOR trials received 13 injections through 12 months, the patients in the PrONTO study received an average of just 5.6 injections with a median of five injections. Other visual acuity efficacy end points were similar as well. In the MARINA and ANCHOR trials, 94.6% and 96.4% of patient respectively avoided a 15-letter visual acuity decrease, whereas in the PrONTO study, 95% of patients avoided such a loss. In the MARINA and ANCHOR trials, 33.8% and 40.3% of patients gained at least 15 letters of visual acuity compared with 35% of patients in the PrONTO study. Finally, when comparing the proportion of patients with zero or more letters gained at 12 months, the MARINA and ANCHOR

FIGURE 8. Case 2: Optical coherence tomography (OCT) response to the first ranibizumab injection from baseline through month 1 in an eye with neovascular age-related macular degeneration (AMD) characterized as retinal angiomatous proliferation. Vertical (Left) and horizontal (Right) OCT scans and central retinal thickness measurements of the left eye are shown at baseline (305 μm; visual acuity [VA]: 20/50), ranibizumab no. 1 injected; day 1 (218 μm); day 2 (216 μm); day 4 (215 μm); day 7 (212 μm); day 14 (183 μm; VA: 20/40); month 1 (172 μm; VA: 20/40); ranibizumab no. 2 injected.



studies reported 71.3% and 77.7%, respectively, whereas the PrONTO study had 82.5% of patients without any letters lost.

While it is encouraging that the results of the PrONTO Study are similar to both the MARINA and ANCHOR trials, there are several differences between the studies that limit such comparisons. In contrast to these large, double-masked, randomized, controlled, Phase III clinical trials, the PrONTO study was a much smaller, open-label, unmasked study. The PrONTO study further differed from the Phase III trials by enrolling a heterogeneous population of neovascular lesions with prior therapy permitted and selected primarily by the presence of macular fluid as detected using OCT. As a result, the PrONTO study included both minimally classic and occult with no classic lesions as in the MARINA trial as well as predominantly classic lesions as in the ANCHOR trial; however, the lesions in the phase III trials were selected based on angiographic criteria and no prior therapy was permitted.

Perhaps it would be more appropriate to compare the PrONTO results alongside the PIER trial, another Phase III ranibizumab trial that included all the major angiographic lesion subtypes of neovascular AMD. [4] In the PIER trial, patients received three scheduled monthly injections as in the PrONTO Study, but after the second month, the PIER protocol followed a fixed dosing regimen of every three months. In contrast to the PrONTO study, the mean visual acuity decreased at month 12 by 0.2 letters. The other secondary visual acuity end points showed a similar decrease in efficacy compared with the MARINA and ANCHOR trials. The most likely explanation for these disappointing outcomes from the PIER trial is the need for more frequent retreatment in some patients as shown from the results of the PrONTO study.

The retreatment criteria chosen for the PrONTO were based on clinical observations made following the completion of the Phase I/II ranibizumab studies and during the extension study when patients could be retreated at the discretion of the investigator. From these observations, it appeared that OCT could detect the earliest signs of recurrent fluid in the macula after the ranibizumab injections were stopped. The signs of recurrent fluid included the appearance of macular cysts or subretinal fluid, and these signs were thought to represent the earliest manifestations of recurrent CNV. The PrONTO study was designed to demonstrate that if these early signs were observed and followed over time, then more fluid would eventually accumulate within the macula, leading to vision loss, hemorrhage, or classic CNV. For this reason, the OCT retreatment criteria chosen for the PrONTO study required that a large amount of fluid reaccumulate in the macula (100 μm) or vision loss occur before retreatment was offered. Although the vast majority of reinjections in the PrONTO used one of the OCT-based criteria, some eyes were reinjected because of new hemorrhage or new classic CNV. However, regardless of the criteria used, the need for retreatment could have been predicted based on qualitative OCT changes alone. Whenever new hemorrhage or new classic CNV was present, the OCT always showed recurrent fluid in the macula, but of a level insufficient to trigger a retreatment based on the criteria used in this study. Even in months before an increase in central retinal thickness of at least 100 μm or a five letter visual acuity decrease associated with fluid in the macula, there were always qualitative changes on the OCT images suggestive of new fluid in the macula. Therefore, one possible strategy for future ranibizumab studies would be to use any qualitative OCT change that suggests recurrent fluid such as the appearance of any cysts or subretinal fluid as the basis for retreatment. Perhaps, current PrONTO results would have been even better if patients had been reinjected as soon as the recurrent fluid was detected by OCT rather than waiting until more fluid accumulated or vision deteriorated.

A direct head-to-head trial will be necessary to unequivocally conclude that a variable dosing regimen using OCT is as good as a fixed monthly dosing regimen, but it is unlikely such a study will ever be performed now that ranibizumab is commercially available, and an ongoing Phase IIIb clinical safety study with more than 2,000 patients uses an open-label, variable-dosing regimen similar to the regimen used in the PrONTO study. This Phase IIIb study is known by the acronym SAILOR.[4] Most likely, future studies with ranibizumab in neovascular AMD will focus on ways to further reduce the overall number of ranibizumab injections while achieving the same or better visual acuity outcomes. This approach will be particularly useful for RAP lesions. A decrease in the number of injections would reduce the potential risk of injection-related complications, and an increase in the injection-free interval

FIGURE 9. Case 2: Optical coherence tomography (OCT) response from baseline through month 6 after ranibizumab injections at month 1, month 2, month 3, and month 5 in an eye with neovascular age-related macular degeneration (AMD) characterized as retinal angiomatous proliferation. Vertical (Left) and horizontal (Right) OCT scans and central retinal thickness measurements are shown of her left eye at baseline (305 μm, visual acuity [VA]: 20/50), ranibizumab no. 1 injected; month 1 (172 μm; VA: 20/40), ranibizumab no. 2 injected; month 2 (172 μm; VA: 20/32), ranibizumab no. 3 injected; month 3 (173 μm; VA: 20/32), observed; month 4 (251 μm; VA: 20/40), observed; month 5 (328 μm; VA: 20/32), ranibizumab no. 4 injected; month 6 (147 μm; VA: 20/32), observed.

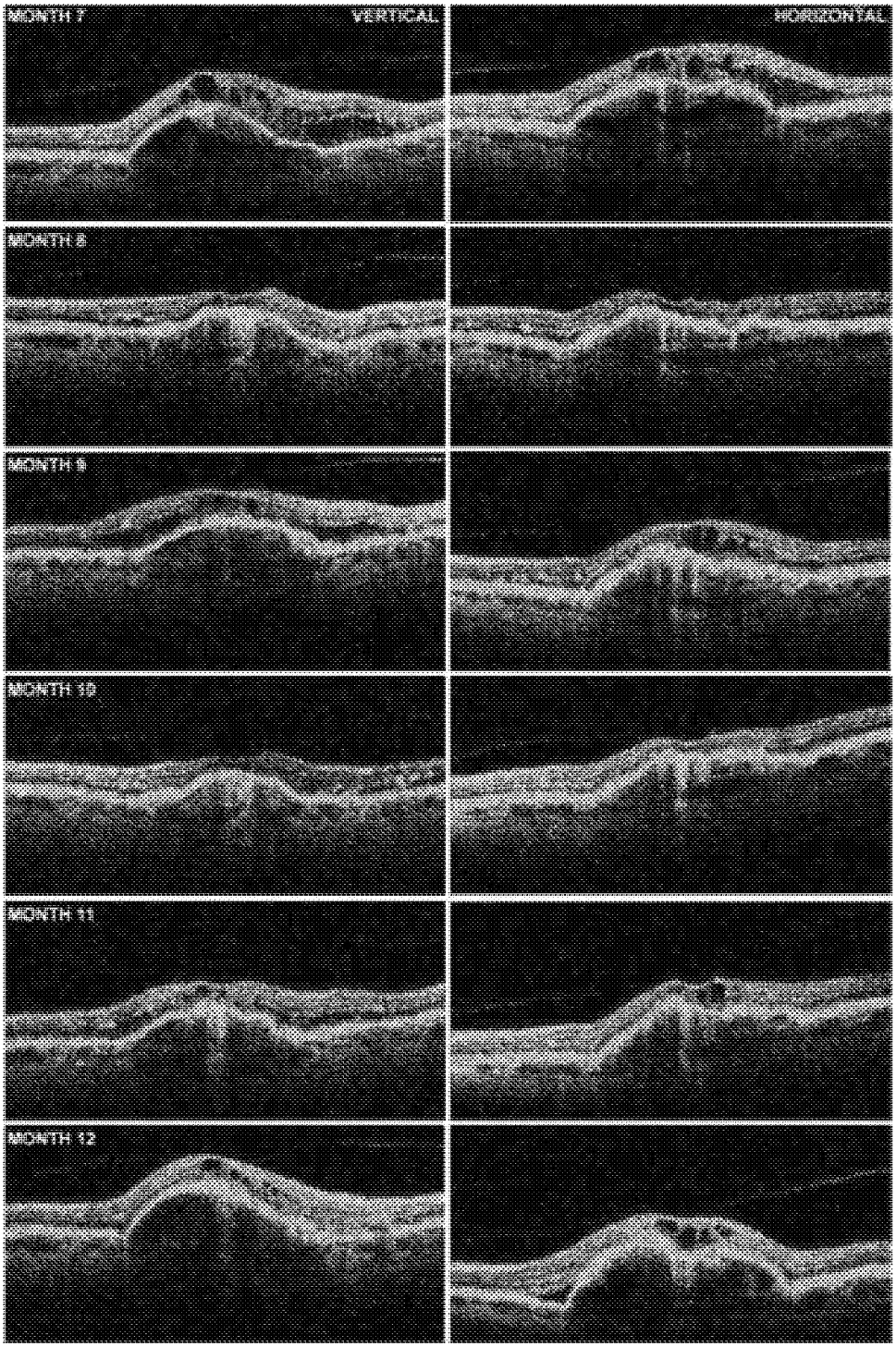


FIGURE 10. Case 2: Optical coherence tomography (OCT) response from month 7 through month 12 after ranibizumab injections at month 7, month 9, and month 12 for a total of seven ranibizumab injections over 12 months in an eye with neovascular age-related macular degeneration (AMD) characterized as retinal angiomatous proliferation. Vertical (Left) and horizontal (Right) OCT scans and central retinal thickness measurements are shown of her left eye at month 7 (277 μm; VA: 20/40), ranibizumab no. 5 injected; month 8 (144 μm; visual acuity [VA]: 20/32), observed; month 9 (277 μm; VA: 20/40), ranibizumab no. 6 injected; month 10 (151 μm; VA: 20/40), observed; month 11 (201μm; VA: 20/40), observed; month 12 (280 μm; VA: 20/50), ranibizumab no. 7 injected.

would reduce the burden of frequent follow-up evaluations.

In conclusion, a variable dosing regimen with ranibizumab resulted in an average of 5.6 injections over one year with visual acuity and OCT improvements that were statistically and clinically significant. These results were similar to the outcomes obtained using 13 monthly injections over one year in the fixed-dosing Phase III regimens. The outcomes from the PrONTO study suggest that OCT can be useful for guiding retreatment with intravitreal ranibizumab in neovascular AMD, and the use of such an OCT-guided, variable-dosing regimen should decrease the injection burden without sacrificing improvements in visual acuity.

THIS STUDY WAS SUPPORTED IN PART BY GENENTECH, INC SOUTH SAN FRANCISCO, CALIFORNIA, AN UNRESTRICTED grant from Research to Prevent Blindness, Inc, New York, New York, NEI core grant P30 EY014801; and by the German Research Foundation (DFG), Bonn, Germany. Drs Fung and Rosenfeld have received additional clinical research grants from Genentech, Inc. Drs Rosenfeld, Fung, Flynn, Jr, and Puliafito have received payment for participating on Genentech Advisory Boards. Drs Rosenfeld and Fung have participated in the Genentech speaker's bureau program and received lecture fees. Dr Rosenfeld has participated in scientific advisory boards from competing companies: Eyetech Pharmaceuticals, Melville, New York, Novartis Ophthalmics, East Hanover, New Jersey, Protein Design Labs, Fremont, California, Allergan, Irvine, California, BioAxone, Saint-Laurent, Quebec, Quark Inc, Fremont, California, Jerini AG, Berlin, Germany, Genaera, Plymouth Meeting, Pennsylvania, Tanox, Houston, Texas, and Athenagen, South San Francisco, California. Dr Fung has participated in scientific advisory boards from competing companies: Eyetech Pharmaceuticals and Santen, Napa, California. Dr Michels has participated in scientific advisory boards from competing companies: Pfizer, New York, New York, and Novartis Ophthalmics. Dr Puliafito has participated in scientific advisory boards from the competing company Eyetech Pharmaceuticals. Dr Davis has participated in scientific advisory boards from the competing company Bausch & Lomb, Rochester, New York. Dr Fynn, Jr, has participated in scientific advisory boards from competing companies: Alcon, Fort Worth, Texas, Allergan, Eyetech Pharmaceuticals, Novartis Ophthalmics, and Lilly, Indianapolis, Indiana. Dr Rosenfeld has indicated support for lecture fees from the following competing companies: Eyetech Pharmaceuticals and Novartis Ophthalmics. Dr Michels has indicated support for lecture fees from the following competing companies: Alcon and Novartis Ophthalmics. Dr Puliafito has indicated support for lecture fees from the following competing company: Eyetech Pharmaceuticals. Dr Flynn, Jr, has indicated support for lecture fees from the following competing companies: Eyetech and Lilly. Dr Rosenfeld has received clinical research grants from the following competing companies: Eyetech Pharmaceuticals, QLT, Inc, Fort Collins, Colorado, Novartis Ophthalmics, and Alcon Laboratories. Dr Davis has received clinical research grants from the following competing companies: Bausch & Lomb, Inspire Pharmaceutical, Durham, North Carolina, and Allergan Pharmaceuticals. Dr Puliafito is designated on a patent for optical coherence tomography and receives royalties. Involved in conception and design of study (P.J.R., S.M., C.A.P.); analysis and interpretation (A.E.F., G.A.L., P.J.R., W.F., M.E.), writing the article (A.E.F., G.A.L., P.J.R., W.F., M.E.); critical revisions (S.R.D., S.M., C.A.P., J.L.D., H.W.F.); final approval (A.E.F., G.A.L., P.J.R., S.R.D., S.M., W.F., C.A.P., J.L.D., H.W.F., M.E.); data collection (A.E.F., G.A.L., P.J.R., S.R.D., S.M., J.L.D., M.E.); provision of patients and resources (P.J.R., S.R.D., C.A.P., J.L.D., H.W.F.); statistical expertise (W.F.); obtaining funding (P.J.R., C.A.P.); literature search (A.E.F., G.A.L., P.J.R., S.M.); and research technical and administrative support (A.E.F., W.F., C.A.P., M.E.).

Both Anne E. Fung, MD, and Geeta A. Lalwani, MD, contributed equally to the success of this clinical study. The authors gratefully acknowledge the following medical retina fellows from the Bascom Palmer Eye Institute for their expert clinical assistance in evaluating the PrONTO patients: Ryan M. Rich, MD, Bascom Palmer Eye Institute, Miami, Florida; Richard C. Lin, MD, PhD, University of Chicago, Department of Ophthalmology, Chicago, Illinois; and Jackie K. Nguyen, MD, Tufts University, Department of Ophthalmology, Medford, Massachusetts.

REFERENCES

1. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al. VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805–2816.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab vs verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444.
4. Preliminary results from a phase IIIb study showed patients with wet AMD treated with Lucentis quarterly experienced a 16-letter benefit over the control group at one year. [press release]. South San Francisco, California: Genentech; June 2, 2006. Available at: http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9747. Accessed Date: August 26, 2006.
5. Chen Y, Wiesmann C, Fuh G, et al. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. J Mol Biol 1999;293:865–881.
6. Heier JS, Antoszyk AN, Pavan PR, et al. Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. Ophthalmology 2006;113:642 e1–e4.
7. Rosenfeld PJ, Heier JS, Hantsbarger G, et al. Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age-related macular degeneration. Ophthalmology 2006;113:632 e1.
8. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials TAP report 1. Arch Ophthalmol 1999;117:1329–1345.

Biosketch

Anne E. Fung, MD, graduated with honors in Chinese Studies and Economics from Wellesley College in 1993 and received her MD from Cornell University Medical College in 1999. After completing residency at Stanford University, she pursued a research fellowship at the Smith Kettlewell Eye Research Institute. In 2005, she completed a Medical Retina fellowship at the Bascom Palmer Eye Institute and returned to San Francisco to join her father at Pacific Eye Associates/California Pacific Medical Center where she continues clinical research in age-related macular degeneration.

Biosketch

Geeta A. Lalwani, MD, is currently a surgical retina fellow at the Bascom Palmer Eye Institute in Miami, Florida. She received an AB from Smith College, and an MD from the MCP-Hahnemann School of Medicine, where she was elected into the Alpha Omega Alpha honor society. She will complete her fellowship in July 2007.

pharmaceutics

MDPI

Review

Pharmacokinetics of Intravitreal Anti-VEGF Drugs in Age-Related Macular Degeneration

Laura García-Quintanilla [1,2,†], Andrea Luaces-Rodríguez [2,3,†], María Gil-Martínez [4], Cristina Mondelo-García [1,2], Olalla Maroñas [5], Víctor Mangas-Sanjuan [6,7], Miguel González-Barcia [1,2], Irene Zarra-Ferro [1,2], Pablo Aguiar [8,9], Francisco J. Otero-Espinar [3,*] and Anxo Fernández-Ferreiro [1,2,3,*]

1 Pharmacy Department, University Clinical Hospital of Santiago de Compostela (SERGAS), 15706 Santiago de Compostela, Spain
2 Pharmacology Group, Health Research Institute of Santiago de Compostela (FIDIS), 15706 Santiago de Compostela, Spain
3 Department of Pharmacology, Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Santiago de Compostela (USC), 15782 Santiago de Compostela, Spain
4 Ophthalmology Department, University Clinical Hospital of Santiago de Compostela (SERGAS), 15706 Santiago de Compostela, Spain
5 Genomic Medicine Group, Galician Public Foundation of Genomic Medicine, Health Research Institute of Santiago de Compostela (FIDIS), 15706 Santiago de Compostela, Spain
6 Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia, 46100 Valencia, Spain
7 Interuniversity Research Institute for Molecular Recognition and Technological Development, Polytechnic University of Valencia, 46100 Valencia, Spain
8 Nuclear Medicine Department, University Clinical Hospital of Santiago de Compostela (SERGAS), 15706 Santiago de Compostela, Spain
9 Molecular Imaging Group, Health Research Institute of Santiago de Compostela (FIDIS), 15706 Santiago de Compostela, Spain
* Correspondence: francisco.otero@usc.es (F.J.O.-E.); anxo.fernandez.ferreiro@sergas.es (A.F.-F.); Tel.: +34-881814878 (F.J.O.-E.); +34-981950000 (A.F.-F.)
† These authors contributed equally to this work.

Received: 30 June 2019; Accepted: 22 July 2019; Published: 31 July 2019

Abstract: Intravitreal administration of anti-vascular endothelial growth factor (VEGF) antibodies has become the standard treatment for Age-Related Macular Degeneration; however, the knowledge of their pharmacokinetics is limited. A comprehensive review of the preclinical and clinical pharmacokinetic data that were obtained in different studies with intravitreal bevacizumab, ranibizumab, and aflibercept has been conducted. Moreover, the factors that can influence the vitreous pharmacokinetics of these drugs, as well as the methods that were used in the studies for analytical determination, have been exposed. These anti-VEGF drugs present different charge and molecular weights, which play an important role in vitreous distribution and elimination. The pharmacokinetic parameters that were collected differ depending on the species that were involved in the studies and on physiological and pathological conditions, such as vitrectomy and lensectomy. Knowledge of the intravitreal pharmacokinetics of the anti-VEGF drugs that were used in clinical practice is of vital importance.

Keywords: vascular endothelial growth factor/antagonists & inhibitors; ranibizumab; aflibercept; bevacizumab; Age-Related Macular Degeneration; pharmacokinetics; intravitreal

1. Introduction

Age-Related Macular Degeneration (AMD) is the leading cause of irreversible visual impairment among individuals over the age of 65 years all around the world (between 30 and 50 million people). It is expected that its prevalence will double in the next few decades, and it is estimated that 280 million people will be affected by 2040 [1,2].

The disease almost always begins as a non-neovascular form of AMD and it may progress to the neovascular form in one or both eyes [3]. A progressive deterioration in the macula characterises the non-neovascular form, which causes central vision loss. The neovascular form is caused by the abnormal development of blood vessels under the macula, leading to the leakage of fluid and blood causing inflammation. The latter form progresses more rapidly, and it can cause severe vision loss within a few months if left untreated [4].

The cause of the disease is multifactorial (i.e. age, ethnic origin and a combination of genetic and environmental factors) [5]. Several treatments for neovascular AMD have been widely studied, such as laser photocoagulation and photodynamic eye therapy with verteporfin, but nowadays the standard treatment consists of intravitreal injections of inhibitors of vascular endothelial growth factor (anti-VEGF). The anti-VEGF monoclonal antibodies that were used to treat AMD include the approved intravitreal administration of pegaptanib, ranibizumab, and aflibercept and the off-label intravitreal administration of bevacizumab and Ziv-aflibercept [6,7].

Nowadays, in clinical practice, it is very difficult to achieve adequate therapeutic drug levels in the vitreous humour through topical ocular or systemic administration, which is mainly due to the existence of physiological barriers. Oral treatments could be an attractive treatment option; however, they have failed to show benefits in combination with intravitreal anti-VEGF treatments and they are still being evaluated in monotherapy [8]. Therefore, intravitreal injections are still the most appropriate method for treating pathologies that affect the posterior segment of the eye [9]. The frequency of administration of anti-VEGF drugs plays a key role, as their administration is currently not standardised in clinical practice and therefore different administration schedules coexist. Fixed regimens were evaluated in pivotal studies [10–12], in which the patients received monthly or bimonthly injections on a continuous basis over the follow up months [10,11,13]. Fixed monthly injections offer the best visual outcome, but this regimen is not commonly followed outside clinical trials due to the increased number of required visits to the ophthalmologist [14]. In addition, the followed regimen can have significant economic repercussions due to the high cost of these treatments [15]. The two most commonly followed treatment regimens are the pro re nata (PRN), which consists of treating if reactivation, and the Treat and Extend (T&E) strategy. The latter consists of a proactive treatment regimen where the key is to treat the patient before the disease activity appears. It was created to reduce the frequency of injections and it is the most accepted treatment regimen [16,17]. T&E consists of a loading phase of three monthly injections, followed by a progressive lengthening of the treatment intervals by one or two weeks as long as no activity is detected [18]. If disease activity is detected during any visit, treatment intervals are reduced to the interval used prior to the extension. A recent meta-analysis has shown that the T&E regime has a mean of 6.9 fewer injections at 24 months when compared to monthly injections yielding similar visual acuity results. Moreover, when compared to the PRN strategy, T&E has revealed an improvement of 6.18 more letters than PRN in terms of visual gains, however a mean of 1.44 more injections was required for the T&E as compared to PRN regimen at 12 months [16].

Normally, the frequency of administration should be based on the half-life of the drug ($t_{1/2}$) in order to achieve a sustained therapeutic drug concentration in the vitreous. Direct determination of the vitreous drug levels requires invasive techniques, and for this reason, these type of studies are limited to the preclinical field [19,20]. Therefore, most clinical pharmacokinetics studies rely on indirect blood measurements, which have been mainly restricted to pivotal studies, which have not been studied in the great majority of post-authorisation trials [21,22]. For these reasons, the information that is available in this field is very limited.

The present review collects the most relevant aspects of the intravitreal pharmacokinetics of anti-VEGF drugs in AMD. For that purpose, an extensive review of the preclinical and clinical pharmacokinetic studies that have been published in this field was carried out. Moreover, information regarding the factors involved in the vitreous distribution and clearance, the methods for the quantification of anti-VEGF antibodies, and the utility of population models have also been compiled.

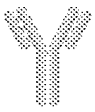
2. Pharmacokinetics of Anti-VEFG Drugs

In is very difficult to perform intravitreal pharmacokinetic studies on humans, given that taking vitreous samples is an invasive procedure; therefore, most of the studies have focused on preclinical research.

2.1. Ranibizumab

Ranibizumab is a fragment of a monoclonal antibody that does not contain the Fc region (heavy chains) and with affinity for all subtypes of VEGF-A (Table 1). It has been approved for the treatment of neovascular AMD based on the results of two clinical trials (ANCHOR and MARINE), where 0.5 mg was administered on a monthly regimen observing improvements in visual acuity with gains of 11.3 letters in the ANCHOR trial and 7.2 letters in the MARINA trial, as compared to the control groups [10,11].

Table 1. Properties of anti-vascular endothelial growth factor (VEGF) antibodies for Age-Related Macular Degeneration (AMD). Data from [23–25].

Properties			
	Ranibizumab	**Bevacizumab**	**Aflibercept**
Class	Antibody fragment	Monoclonal antibody	Fusion protein
MW (KDa)	48	149	115
Net charge	Negative	Negative	Slightly positive
Binding target	VEGF-A	VEGF-A	VEGF-A, VEGF-B, PIGF
K_D for $VEGF_{165}$ (pM)	46	58	0.49

M_w = molecular weight; K_D = equilibrium dissociation constant.

2.1.1. Animal Studies

In a pharmacokinetic analysis that was performed by Bakri et al., 0.5 mg of ranibizumab was intravitreally injected in the right eye of male Dutch-belted rabbits. While using a non-compartment model, they determined that the half-life of ranibizumab was 2.88 days in the vitreous humour and 2.84 days in the aqueous humour. The mean resident time (MRT) was 4 and 6.8 days in vitreous and aqueous humour, respectively, and no serum concentrations were detected [21].

Other studies have found vitreous half-lives within the same range. A study using I-124 labelled ranibizumab in rabbits and quantified by PET/CT obtained a similar vitreous half-life (2.81 days), but a two-compartment model was applied in this case [26]. Another study calculated a vitreous half-life of 2.75 days with a one-compartment model [27]. In all the aforementioned studies of the pharmacokinetics of ranibizumab in rabbits, the standard dose of ranibizumab (0.5 mg/0.05 mL) was injected in just one rabbit eye (unilateral injection). However, the authors of the following study decided to perform a bilateral injection, with a different dose to the standard. They injected 0.625 mg/0.05 mL in both eyes, obtaining a vitreous half-life of 2.9 days with a one-compartment model [28], which is comparable to the half-life that was calculated in the other conditions.

Other studies have tested ranibizumab pharmacokinetics in monkeys as a non-human primate model. Christoforidis et al. performed a study with owl monkeys with I-124 radiolabelled ranibizumab

in the same way as they performed the study in rabbits [26,29]. They obtained a vitreous half-life of 2.73 days after a single intravitreal injection of 0.5 mg/0.05 mL in one eye. Another study, in this case with cynomolgus monkeys, was performed with a bilateral single injection of ranibizumab, while testing two different injection doses: 0.5 mg/0.05 mL and 2 mg/0.05 mL [30]. They obtained vitreous half-lives with a one-compartment model of 2.63 and 3.95 days, respectively. The comparison between both groups suggests dose-linear vitreous pharmacokinetics. Aqueous humour, retina, and serum half-lives were also calculated (with a non-compartmental analysis), obtaining values of 2.54, 2.60, and 3.59 days for the injected dose of 0.5 mg, and 2.63, 2.28, and 3.47 days for the 2 mg injected dose, respectively. They also concluded that ranibizumab rapidly distributes to the retina, and it is removed from the vitreous humour through the anterior chamber (ranibizumab was found in the aqueous humour) and the posterior route (ranibizumab was found in both retinal layers). Moreover, they suggested that intraocular metabolism does not play a significant role in the elimination of ranibizumab from the vitreous chamber [30]. Even though Christoforidis and Gaudreault's studies differ in the monkey species used and the uni/bilateral injection at the dose of 0.5 mg, the estimated vitreous half-lives are comparable (2.73 days vs 2.63 days) [29,30].

2.1.2. Human Studies

A population approach of non-linear pharmacokinetic modelling that is based on serum samples that were collected from patients with AMD enrolled in five clinical trials, receiving from 0.3 to 2 mg per eye of single or multiple intravitreal ranibizumab estimated a vitreous half-life of nine days [22]. Ranibizumab reached maximum serum concentration approximately 0.5 days after intravitreal administration and these concentrations were 90,000 times lower than those that were estimated to be found in the vitreous humour [22]. The estimated serum half-life was two hours, because it is not a full-length antibody and it lacks the FcRn (the neonatal Fc receptor for IgG) that protects from lysosomal degradation, ranibizumab is prone to systemic metabolism [22]. Another study performed three intravitreal injections of ranibizumab (0.5 mg) in AMD patients at monthly intervals. A serum half-life of 5.8 days was calculated after measuring serum levels. They also found that ranibizumab did not demonstrate systemic accumulation between the first and third dose, concluding that ranibizumab is very quickly cleared from the bloodstream [19,31].

Aqueous humour half-life was calculated in the study performed by Krohne et al. They included patients that were diagnosed with both clinically significant cataract and macular oedema secondary to AMD, diabetic maculopathy, or retinal vein occlusion. The patients received a single intravitreal injection (0.5 mg) within 40 days before surgery, in which the aqueous samples were obtained, obtaining an aqueous half-life of 7.19 days. Moreover, they performed axial length measurements of the ocular globe in order to correct ranibizumab concentrations for ocular volume, determining that volume differences did not significantly alter the aqueous half-life (7.15 days) [32].

There is no data available with regards to the vitreous levels of ranibizumab after intravitreal injection in humans, and consequently vitreous half-life values are no available. One group applied a mathematical model that was intended for intravitreal pharmacokinetics in rabbits to estimate the vitreous half-life of ranibizumab in humans. They calculated a vitreous half-life for ranibizumab of 4.75 days while using an experimentally determined mean half-life of bevacizumab in humans [33].

No significant reductions have been observed in the concentration of systemic VEGF levels between baseline and after intravitreal injections of ranibizumab [34–38] or drug accumulation between doses [31].

2.2. Bevacizumab

Bevacizumab is a full monoclonal antibody (with Fc fraction) with an affinity for all subtypes of VEGF-A and systemic indication in the treatment of different types of cancer (breast, colon . . .) (Table 1). There is no current indication for AMD, but its mechanism of action and its administration at the level of the posterior chamber of the eye at a much lower dose (1.25 mg/0.05 mL) have promoted its off-label

use [39]. In addition, the possibility of splitting up the vial in the pharmacy departments reduces the cost of the treatment in comparison with the other two drugs that do have the indication [40].

2.2.1. Animal Studies

Bevacizumab vitreous half-life has been estimated at 4.32 days, following a 1.25 mg/0.05 mL unilateral intravitreal injection in rabbit eyes (non-compartmental analysis), with concentrations that remain above 10 μg/mL for 30 days [41]. The estimated half-life was 4.88 days and 6.8 days in the serum while using the same non-compartment model in the aqueous humour [41]. This data is consistent with the intravitreal pharmacokinetics that were analysed by molecular imaging with I-125-bevacizumab in a rabbit model ($t_{1/2}$ = 4.22 days, two-compartment model) [26]. Bakri et al. found that bevacizumab concentration was higher in the aqueous humour of the fellow eye (uninjected) than in the vitreous, concluding that bevacizumab enters the fellow eye from the systemic circulation through the anterior route, reaching the aqueous humour first before diffusing into the vitreous, rather than entering through the choroidal blood flow [41]. However, very low concentrations of bevacizumab were found in the aqueous and vitreous humour of the uninjected eye, so this conclusion must be taken with caution.

Higher vitreous half-life values (5.95 days) were obtained in the study that was performed by Nomoto et al. in a rabbit model (unilateral injection). They also measured the amount of bevacizumab in iris/ciliary body and retina/choroids, obtaining half-lives in these tissues of 5.74 and 6.23 days, respectively. However, the higher half-lives that were obtained can be explained, because they performed an Enzyme-Linked ImmunoSorbent Assay (ELISA) that detected all bevacizumab, i.e., free bevacizumab, VEGF-bevacizumab complex and fragments of bevacizumab molecules, whereas the majority of the studies only measure free bevacizumab levels, as they have been considered as a good representation of total drug concentration. Moreover, their first sample taken was seven days after injection, so early data is missing in this study, which could counterfeit the results [42].

Another study has found even higher half-lives in vitreous, aqueous humour, and serum (6.61 days, 6.51 days, 5.87 days, non-compartmental analysis) when compared to the other studies of 1.25 mg/0.05 mL bevacizumab unilateral injection in rabbit models [43]. They used New Zealand rabbits instead of Dutch-belted rabbits, together with a high sensitivity ELISA (detection limit 0.001 ng/mL) detection kit, which could explain the differences that were found. However, when compared to Bakri's work, both of the studies found that the maximum concentration was achieved at one day post-injection in the vitreous humour and after eight days in serum [41,43]. One great advantage of this study is that anti-bevacizumab antibodies in serum were also measured, concluding that these anti-bevacizumab antibodies cannot have an important effect on bevacizumab concentration due to their low concentration [43].

The intravitreal half-life estimated in owl monkeys of 1.25 mg/0.05 mL I-124-bevacizumab intravitreal injection was 3.6 days, with detectable concentrations up to 28 days [26]. The pharmacokinetics of bevacizumab in cynomolgus monkeys was also tested by ELISA, but in this case only aqueous humour and serum samples were collected, obtaining half-lives of 2.8 and 12.3 days, respectively [44], preventing the comparison of both studies.

No activity was detected in other parts of the rabbit body apart from the ocular globe in the studies that were performed by Christoforidis et al. with I-125 radiolabelled antibodies bevacizumab, ranibizumab, and aflibercept [26,45]. However, these results are inconsistent with other studies, where bevacizumab was detected in the brain, heart, and kidney after a single intravitreal injection [46].

2.2.2. Human Studies

Vitreous half-life was estimated to be 6.7 days following a two-compartment model. Patients received a single dose of 1.25 mg bevacizumab prior to vitrectomy. A peak concentration of 165 μg/mL was reached on the second day after the intravitreal injection [47]. Another author found that the vitreous half-life ranged between 2.5 and 7.3 days, with a mean of 4.9 days, after the administration of 1.25 mg/0.05 mL while using a one-compartmental model. The vitreous samples were

taken during pars plana vitrectomy [34]. These results should be taken with caution, as only eleven [47] and three [34] patients, respectively, were used for the pharmacokinetic analysis. Moreover, the fact that vitrectomy was performed due to collateral complications, such as submacular haemorrhage and choroidal neovascularization [47] or cataract extraction [34] must also be taken into account. The latter study also evaluated the serum half-life of bevacizumab, determining it to be 11.3 days [34].

A serum half-life of 18.7 days [19,31] has been estimated after three-single intravitreal doses of 1.25 mg of bevacizumab. Moreover, its systemic exposure was found to be greater than that og ranibizumab or aflibercept, with a serum concentration of 1.58 nM, which is higher than the estimated inhibitory concentration (IC50) for VEGF factor (IC50 = 0.668 nM) [48]. This data suggests the possibility of adverse effects that are usually associated with the intravenous doses of these drugs, and that could appear in patients with AMD, macular oedema, etc. [49–51].

Aqueous half-life was estimated to be 9.82 days in humans by non-compartmental analysis. Patients received a single intravitreal injection of 1.5 mg bevacizumab and within 53 days after the injection, an aqueous humour sample was obtained during cataract surgery. The patients were diagnosed with cataract and recurrent macular oedema secondary to AMD. Bevacizumab concentration peaked on the first day, with a mean concentration of 33.3 μg/mL [52].

The same dose (1.5 mg) was administered in another study and was compared to a higher dose of 3 mg. The maximum concentration in the aqueous humour was obtained at one day post-injection for both doses, with an aqueous half-life of 7.85 and 11.69 days for the 1.5 and 3 mg doses, respectively, calculated by one-compartmental analysis. Double dosing induced a significant higher peak concentration at baseline, although the aqueous bevacizumab concentration was not significantly different after six weeks. Therefore, the administration of a double-dose does not significantly increase the duration of action. This study presents several limitations, as that the enrolled patients suffered from different retinal diseases and the injection volume was double for the dose of 3 mg in relation to 1.5 mg, which could affect the pharmacokinetic parameters [53].

Regarding the bevacizumab levels in the aqueous humour of the uninjected eye, the study that was conducted by Meyer et al. found that the concentration of bevacizumab was below the ELISA detection limit, so no significant levels are expected to be found in the fellow aqueous chamber [54].

2.3. *Aflibercept*

Aflibercept has a different mechanism than the other two. It is a recombinant fusion protein that consists of portions from the extracellular domains of the human VEGF receptors 1 and 2, which are fused with the Fc portion of the human IgG1. Aflibercept has a great affinity for VEGF A, B, and placental growth factor (P1GF) (Table 1). The data on the pharmacokinetics of aflibercept is scarce and mostly refers to animal models in comparison with the other two anti-VEGF drugs.

2.3.1. Animal Studies

Christoforidis et al. also performed studies with I-124 radiolabelled aflibercept, obtaining a vitreous half-life of 4.58 days after a single intravitreal injection of 2 mg/0.05 mL in Dutch-belted rabbits [45]. Another study found a vitreous half-life of 3.92 days in New Zeeland white rabbits [55]. The differences could be due to the fact that the aflibercept concentration was quantified by an indirect ELISA and the dose injected was lower, 1.2 mg/0.03 mL. In this study, the aqueous humour and retina/choroid half-lives were also calculated, which obtained values of 2 and 2.425 days, respectively [55].

Studies in owl monkeys were also performed with I-124 aflibercept, obtaining a vitreous half-life value of 2.44 days [29], whereas the vitreous half-life value was 2.2 days in cynomolgus macaques where aflibercept concentration was measured by ELISA [56].

2.3.2. Human Studies

Serum half-life of aflibercept has been estimated at 11.4 days after three-monthly intravitreal injections of aflibercept (2.0 mg) in an AMD population. The authors found that aflibercept seemed to exhibit systemic drug accumulation between the first and third dose [19,31].

Some of the authors explored the relation between systemic exposure to intravitreal aflibercept injection and systemic pharmacodynamics (blood pressure). They included patients from four different clinical trials. Aflibercept plasma concentrations quickly decreased over a week to concentrations below the LLOQ (15.6 µg/L) once peak concentrations has been achieved within 1–3 days post-dose. Intravitreal administrations were not associated with common adverse effects of intravenous anti-VEGF [57].

The authors of this article suggest, that owing to the intermediate size of aflibercept (between ranibizumab and bevacizumab), the vitreous half-life of aflibercept could be hypothesised to be nine days since no intravitreal pharmacokinetic studies have been performed in humans with aflibercept [58]. A study conducted in five patients with AMD found an aqueous half-life of approximately nine days based on aqueous samples. They also found very low plasma levels, suggesting a lack of substantial plasma exposure [59].

The same author that calculated a vitreous half-life of ranibizumab in humans with a mathematical model, determining a vitreous half-life of 7.13 days for aflibercept following the same procedure [33].

A compiled list of the different pharmacokinetic parameters analysed in the studies of ranibizumab (Table 2), bevacizumab (Table 3), and aflibercept (Table 4) in different species (rabbit, monkey, and human) has been included at the end of this section. The compiled parameters include half-life ($t_{1/2}$), time taken to reach maximum concentration (T_{max}), maximum concentration (C_{max}), and area under the concentration-time curve (AUC). C_{max} is reached very early on due to the rapid distribution of the antibodies through the vitreous humour, so most of the studies assume that their first data point (normally one day post-injection) corresponds to T_{max}. Therefore, the utility of defining T_{max} is sometimes controversial. However, T_{max} is shown in the pharmacokinetic tables in order to provide a time reference corresponding to C_{max}.

Table 2. Pharmacokinetic parameters of intravitreal ranibizumab in different species.

Model	Injected Dose	Determination	Sensitivity	PK Model	Sample	Time Points	Normal Eyes				Vitrectomy			Aphakia	Observations	Ref.
							$t_{1/2}$	T_{max}	C_{max}	AUC	$t_{1/2}$	C_{max}	AUC	$t_{1/2}$		
Dutch-belted rabbits	0.5 mg/0.05 mL	CLIA	LLOQ = 0.375 ng/mL	NC	VH	1, 3, 8, 15, 29 days	2.88 days	1 day	162 µg/mL						No detection in serum	[21]
					AH		2.84 days	3 days	17.9 µg/mL							
					Serum											
Dutch-belted rabbits	0.5 mg/0.05 mL	PET (I-124)		2C	VH	0, 2, 5, 7, 14, 21, 28, 35 days	2.81 days	0 h							No detection in other organs	[28]
					AH											
					Serum											
Dutch-belted rabbits	0.5 mg/0.05 mL	PET (I-124)		2C	VH	0, 2, 5, 7, 14, 21, 28, 35 days	2.81 days				2.13 days			1.79 days		[68]
					AH											
					Serum											
New Zealand rabbits	0.625 mg/0.05 mL	ELISA	0.78 ng/mL	1C	VH	1, 8 h; 1, 2, 4, 7, 14, 21, 30, 42, 50, 60 days	2.9 days	1 h	1280 µg/mL						Bilateral injection	[28]
			0.78 ng/mL	NC	AH		3 days	48 h	57.1 µg/mL							
			7.8 ng/mL	NC	Serum			24 h	0.055 µg/mL							
New Zealand rabbits	0.25 mg/0.025 mL	ELISA	LLOQ = 0.375 ng/mL	1C	VH	1 h or 1, 2, 5, 14, 30 days	2.75 days	1 h	91.61 µg/mL		2.51 days	118.01 µg/mL				[27]
					AH			1 h	20.38 µg/mL			21.7 µg/mL				
					Serum											
Owl monkeys	0.5 mg/0.05 mL	PET (I-124)		2C	VH	0, 1, 2, 4, 8, 14, 21, 28, 35 days	2.73 days									[29]
					AH											
					Serum	1, 2, 4, 8, 12 h; 1, 2, 4, 8, 14, 21, 28, 35 days		24 h	0.47 ng/mL							
Cynomolgus macaques	0.5 mg/0.05 mL	ELISA	1.5 ng/mL	1C	VH	6 h, 2, 3, 5, 8, 11 days	2.63 days	6 h	169 µg/mL						Bilateral injection	[38]
			1.5 ng/mL	NC	AH		2.54 days	6 h	116 µg/mL							
			15.6 ng/mL	NC	Serum	2, 6, 12, 24, 36, 48 h; 4–11 days	3.59 days	6 h	150 µg/mL							
Cynomolgus macaques	2 mg/0.05 mL	ELISA	1.5 ng/mL	1C	VH	6 h, 2, 3, 5, 8, 11 days	3.95 days	1 day	612 µg/mL						Bilateral injection	[38]
			1.5 ng/mL	NC	AH		2.63 days	1 day	478 µg/mL							
			15.6 ng/mL	NC	Serum	2, 6, 12, 24, 36, 48 h; 4–11 days	3.47 days	6 h	616 µg/mL							
Cynomolgus macaques	0.25 mg/0.05 mL	ELISA	LLOD = 156 pg/mL	1C	VH	1, 3 days; 1–8 weeks										[56]
					AH		2.3 days	1 day	51.3 µg/mL	171 days ·µg/mL	1.4 days	41.8 µg/mL	154 days ·µg/mL			
					Serum											

Table 2. *Cont.*

Model	Injected Dose	Determination	Sensitivity	PK Model	Sample	Time Points	Normal Eyes				Vitrectomy			Aphakia	Observations	Ref.
							$t_{1/2}$	T_{max}	C_{max}	AUC	$t_{1/2}$	C_{max}	AUC	$t_{1/2}$		
Human	0.5 mg/0.05 mL	ELISA	10–1000 ng/mL	1C	VH	1–37 days										[32]
					AH		7.19 days	1 day	56.1 µg/mL							
					Serum											
Human	Variable	CLIA	LLOQ = 0.3 ng/mL	1C	VH	Variable	9 days									[23]
					AH											
					Serum		2 h									
Human	0.5 mg/0.05 mL	ELISA	LLOQ = 15 pg/mL	NC	VH	3 h; 1, 3, 7, 28 days										[12,31]
					AH											
					Serum		5.8 days		0.11 nM	0.46 h·nM						

CLIA = Chemoluminiscent immunoassay; ELISA = Enzyme-Linked ImmunoSorbent Assay; PET = Positron Emission Tomography; LLOD = Lower Limit of Detection, LLOQ = Lower Limit of Quantification, 1C = One-compartment model; 2C = Two-compartment model; NC = Non-compartment model; VH = vitreous humour; AH = aqueous humour; $t_{1/2}$ = half-life; T_{max} = time taken to reach maximum concentration; C_{max} = maximum concentration; AUC = area under the curve.

Table 3. Pharmacokinetic parameters of intravitreal bevacizumab in different species.

Model	Injected Dose	Determination	Sensitivity	PK Model	Sample	Time Points	Normal Eyes			Vitrectomy				Aphakia	Observations	Ref.
							$t_{1/2}$	T_{max}	C_{max}	AUC	$t_{1/2}$	C_{max}	AUC	$t_{1/2}$		
Dutch-belted rabbits	1.25 mg/0.05 mL	CLIA	LLOQ = 0.0625 ng/mL	NC	VH	1, 3, 8, 15, 29 days	4.32 days	1 day	400 µg/mL							[33]
					AH		4.88 days	3 days	37.7 µg/mL							
					Serum		6.86 days	8 days	3.33 µg/mL							
Dutch-belted rabbits	1.25 mg/0.05 mL	ELISA	LLOQ = 0.1 ng/mL		VH	1, 2, 4, 12 weeks	5.95 days	7 days	59.7308 µg/mL							[32]
					AH			7 days	373.6 ng/mL							
					Serum		12.95 days	14 days	2.0872 µg/mL							
Dutch-belted rabbits	1.25 mg/0.05 mL	PET (I-124)		2C	VH	0, 2, 5, 7, 14, 21, 28, 35 days	4.22 days	0 h							No detection in other organs	[28]
					AH											
					Serum											
Dutch-belted rabbits	1.25 mg/0.05 mL	PET (I-124)		2C	VH	0, 2, 5, 7, 14, 21, 28, 35 days	4.22 days				2.30 days			2.08 days		[63]
					AH											
					Serum											
Dutch-belted rabbits	1.25 mg/0.05 mL	ELISA	LLOD = 10 ng/mL	1C	VH	2, 4, 7, 10, 14, 21, 28, 35 days										[64]
					AH											
					Serum		6.69 days	6.4 days	6.22 µg/mL	69.2 d·µg/mL	2.80 days	6.19 µg/mL	84.1 d·µg/mL	1.41 days		
New Zealand rabbits	1.25 mg/0.05 mL	ELISA	LLOD = 0.01 ng/mL	NC	VH	1, 3, 8, 15, 29 days	6.61 days	1 day	406.25 µg/mL							[33]
					AH		6.51 days	1 day	5.835 µg/mL							
					Serum		5.87 days	8 days	0.413 µg/mL							
New Zealand rabbits	1.25 mg/0.05mL	ELISA	LLOQ = 0.0625 ng/mL	1C	VH	1 h; 1, 2, 5, 14, 30 days	7.06 days	1 h	1021.54 mg/mL		6.99 days					[62]
					AH			2 days	121 mg/mL							
					Serum											
New Zealand rabbits	0.025 mL	PET (Zr-89)			VH	5–60 min; 4, 24, 48, 120, 144 h	3.51 days									[52]
					AH											
					Serum											
Owl monkeys	1.25 mg/0.05 mL	PET (I-124)		2C	VH	0, 1, 2, 4, 8, 14, 21, 28, 35 days	3.60 days									[23]
					AH											
					Serum	1, 2, 4, 8, 12 h; 1, 2, 4, 8, 14, 21, 28, 35 days		3.5 days	7.80 ng/mL							
Cynomolgus macaques	1.25 mg/0.05 mL	ELISA	LLOD = 0.156 ng/mL		VH	1, 3, 7 d; 2, 4, 6, 8 weeks										[43]
					AH		2.8 days	1 day	49.500 µg/mL							
					Serum		12.3 days	7 days	1.430 µg/mL							

Table 3. *Cont.*

Model	Injected Dose	Determination	Sensitivity	PK Model	Sample	Time Points	Normal Eyes				Vitrectomy			Aphakia	Observations	Ref.
							$t_{1/2}$	T_{max}	C_{max}	AUC	$t_{1/2}$	C_{max}	AUC	$t_{1/2}$		
Cynomolgus macaques	1.25 mg/0.05 mL	ELISA	7.8–1000 pg/mL		VH	1, 3, 7 d; 2, 4, 6, 8 weeks										[68]
					AH			1 day	10.8 µg/mL		1.5 days					
					Serum		5.9 days	1 day	42.2 ng/mL							
Human	1.25 mg/0.05 mL	ELISA	LLOQ = 313 pg/mL	NC	VH	3 h; 1, 3, 7, 28 days										[39,31]
					AH											
					Serum		18.7 days		0.76 nM	16.10 h·nM						
Human	1.25 mg/0.05 mL	ELISA		2C	VH	1–101 days	6.7 days	2 days	165 µg/mL	2036 d·µg/mL						[47]
					AH											
					Serum											
Human	1.25 mg/0.05 mL	ELISA	6.25 ng/mL		VH	Variable	4.9 days				0.66 day					[34]
					AH											
					Serum		11.3 days									
Human	1.5 mg	ELISA		1C	VH	1–53 days										[32]
					AH		9.82 days	1 day	33.3 µg/mL							
					Serum											
Human	1.5 mg	ELISA		1C	VH	1–60 days										[33]
					AH		7.85 days	1 day	14.86 µg/mL							
					Serum											
Human	3 mg	ELISA		1C	VH	1–60 days										[33]
					AH		11.69 days	1 day	27.74 µg/mL							
					Serum											

CLIA = Chemoluminiscent immunoassay; ELISA = Enzyme-Linked ImmunoSorbent Assay; PET = Positron Emission Tomography; LLOD = Lower Limit of Detection, LLOQ = Lower Limit of Quantification, 1C = One-compartment model; 2C = Two-compartment model; NC = Non-compartment model; VH = vitreous humour; AH = aqueous humour; $t_{1/2}$ = half-life; T_{max} = time taken to reach maximum concentration; C_{max} = maximum concentration; AUC = area under the curve.

Table 4. Pharmacokinetic parameters of intravitreal aflibercept in different species.

Model	Injected dose	Determination	Sensitivity	PK Model	Sample	Time Points	Normal Eyes				Vitrectomy			Aphakia	Observations	Ref.
							$t_{1/2}$	T_{max}	C_{max}	AUC	$t_{1/2}$	C_{max}	AUC	$t_{1/2}$		
Dutch-belted rabbits	2 mg/0.05 mL	PET (I-124)		1C	VH	0, 2, 5, 7, 14, 21, 28, 35 days	4.58 days	0 h							No detection in other organs	[35]
					AH											
					Serum											
Owl monkeys	2 mg/0.05 mL	PET (I-124)		2C	VH	0, 1, 2, 4, 8, 14, 21, 28, 35 days	2.44 days									[29]
					AH											
					Serum	1, 2, 4, 8, 12 h; 1, 2, 4, 8, 14, 21, 28, 35 days		2 days	3.50 ng/mL							
Cynomolgus macaques	2 mg/0.05 mL	ELISA	LLOD = 156 pg/mL	1C	VH	1, 3 days; 1–8 weeks										[36]
					AH		2.2 days	1 day	74 µg/mL	174 d·µg/mL	1.5 days	68 µg/mL	124 d·µg/mL			
					Serum											
Human	2 mg/0.05 mL	ELISA	LLOQ = 1000 pg/mL	NC	VH	3 h; 1, 3, 7, 28 days										[32,33]
					AH											
					Serum		11.4 days		0.45 nM	4.32 h·nM						
Human	2 mg	ELISA			VH	4 h; 1, 3, 7, 14, 28 days										[38]
					AH		11 days	4 h	64.4 mg/L							
					Serum			4 h	0 mg/L							

CLIA = Chemoluminiscent immunoassay; ELISA = Enzyme-Linked ImmunoSorbent Assay; PET = Positron Emission Tomography; LLOD = Lower Limit of Detection, LLOQ = Lower Limit of Quantification, 1C = One-compartment model; 2C = Two-compartment model; NC = Non-compartment model; VH = vitreous humour; AH = aqueous humour; $t_{1/2}$ = half-life; T_{max} = time taken to reach maximum concentration; C_{max} = maximum concentration; AUC = area under the curve.

3. Pharmacokinetic Considerations

Many factors are involved in the pharmacokinetics of anti-VEGF antibodies, from the physiological conditions of the eye, to the surgical procedures or the analytical methods, which allow for their determination.

3.1. Eye Physiological Factors

3.1.1. Distribution-Diffusion in the Vitreous Humour

The distribution of drugs in the vitreous humour is conditioned by its intrinsic characteristics, such as volume and composition, as well as by the properties of the drug (charge, molecular weight, and protein binding capacity). The vitreous humour occupies around 80% of the internal volume of the eye, which is around 4 mL in humans, 1.5 mL in rabbits, and 2 mL in monkeys [65]. It is an avascular structure that is mainly composed of a hydrophilic polymer of hyaluronic acid and collagen, which contributes to its consistency and attracts water, which is its majority component (98%). The central part of the vitreous humour has less of these components than the posterior part, which makes it more fluid-like. In addition, hyaluronic acid has a negative charge, meaning that the restrictive diffusion of positively charged molecules may occur [66]. Bevacizumab and ranibizumab are both negatively charged molecules under physiological conditions, therefore their movement should not be restricted in the vitreous humour [24]. However, aflibercept is considered to have a mild positive charge, which might affect its pharmacokinetic properties [25].

On other hand, molecular weight affects drug diffusion, which therefore affects the half-life. The anti-VEGF molecules are rather heavy molecules (149 KDa, 115 KDa, 48 KDa for bevacizumab, aflibercept, and ranibizumab, respectively), so they are expected to have a low intravitreal clearance when compared with small molecules that do not have steric hindrance (in general, intravitreal half-life increases as molecular weight rises above 10,000 Da) [67]. A comparison of the properties of the three anti-VEGF inhibitors can be found in Table 1 [23–25].

Moreover, the rheological properties of the vitreous humour change with age, in a process called liquefaction, in which the vitreous humour is turned into a more liquefied state. Liquefaction might increase drug diffusion, especially in those with high molecular weight [67]. When compared to plasma, the concentration and number of proteins in the vitreous humour is low (0.5–1.5 mg/mL in vitreous vs 60–80 mg/mL in plasma) [68]. The main proteins are collagen (a structural protein), albumin, and immunoglobulins (non-structural proteins) [69]. The binding of drugs to proteins might reduce its distribution through the vitreous humour, although this factor does not seem to affect the diffusion of anti-VEGF drugs [70].

3.1.2. Elimination of Drugs from the Vitreous Humour

The elimination of drugs from the vitreous humour can occur via two different routes, either by metabolism or by disposal into the systemic circulation. In the case of the anti-VEGF drugs, they do not appear to suffer metabolism nor degradation in the eye [58,70].

After intravitreal injection, the drugs can be removed to the systemic circulation by two routes: the anterior route or the posterior route. The anterior route consists of drug diffusion through the vitreous humour until it reaches the aqueous humour and it is then eliminated through its flow. All the drugs can be eliminated in this way. Various reports have considered that anti-VEGF drugs are mainly eliminated through the anterior route [21,28,32,52,71].

The posterior route consists of the secretion of the drug by the epithelium of the ciliary body, iris, or retinal pigment epithelium [70]. Peters and Heidushka tried to demonstrate that bevacizumab was also eliminated through the posterior route crossing the blood-retinal barrier. They observed that bevacizumab immunoreactivity after the intravitreal injection extended over time to the inner layers of the retina. However, they did not attempt to determine whether or not active transport is involved in

this process [72,73]. The effect of active transport through the retina is not yet clear, so the impact that this may have on the drug pharmacokinetics is yet to be defined [74].

3.2. Surgical Ocular Procedures (Lensectomy and Vitrectomy)

The distribution and elimination of anti-VEGF drugs from the vitreous are intimately related to several ophthalmic surgical procedures. Laude et al. suggest that cataract operated patients could have a faster clearance of vitreous drugs [67]. However, Krohne et al. found that ocular volume and lens status have no relevant impact on ocular pharmacokinetics and the duration of action of anti-VEGF drugs after comparing VEGF suppression times in phakic (natural lens) and pseudophakic (replaced crystalline lens) human eyes [75].

On the other hand, many patients with macular disease who are being treated with anti-VEGF drugs require surgical intervention for complications, such as bleeding in the vitreous. It is known that replacing the gel-like vitreous humour with a less viscous saline or aqueous humour facilitates the transportation of oxygen, as well as the clearance of VEGF inhibitors and cytokines, reducing oedema and retinal neovascularisation [76,77]. Additionally, the surgical procedure itself and the use of silicone oil as vitreous replacement can influence drug pharmacokinetics [78].

There are few studies that correlate the effect of vitrectomy with the pharmacokinetics and these give very different results. A study performed on rabbits with labelled mAbs with I-124 demonstrated a reduction in the half-life of anti-VEGF drugs after vitrectomy and lensectomy, going from 4.22 to 2.30 and 2.08 days, respectively, for bevacizumab and from 2.81 to 2.13 and 1.79 days, respectively, for ranibizumab [60]. The same author also quantified the serum concentration of bevacizumab in rabbits, finding that the serum levels initially increased following the vitrectomy, but determining that there were not any significant differences later on [61]. On the contrary, other authors did not find significant differences on the vitreous half-life on injected bevacizumab in non-vitrectomised vs vitrectomised eyes in rabbit eyes (7.06 days vs 6.99 days) [62], which suggested that VEGF is a complex molecule that is not restricted to the elimination by diffusion. However, they did find that vitrectomy affected the PK parameters in the initial distribution phase in a two-phase fitting [62]. Another study that was published by the same author on ranibizumab also showed no differences between the vitreous half-life in normal rabbit eyes (2.75 days) and following the vitrectomy (2.51 days) [27]. In this case, the parameters were established according to one-phase kinetics.

After a vitrectomy, filling the vitreous cavity with a tamponade, such as silicone oil, is a common procedure. The impact of silicone-oil filled eyes in the pharmacokinetics of injected bevacizumab was studied, observing longer T_{max}, smaller C_{max}, and relatively sustained bevacizumab levels in the ocular tissues in comparison with non-vitrectomised rabbit eyes [79].

Niwa et al. calculated the aqueous half-life of intravitreally injected ranibizumab and aflibercept in macaque eyes, even though the majority of the studies were performed in rabbit model. They found that the aqueous half-life was reduced after the vitrectomy (from 2.3 to 1.4 days for ranibizumab and from 2.2 to 1.5 days for aflibercept) [56]. However, these results must be taken with caution, due to the fact that the aqueous half-life might be not comparable to the vitreous half-life.

In summary, there is evidence of a decrease in the half-life of intravitreal injected antibodies after vitrectomy is performed, although it is not quite clear whether or not these differences are relevant enough to change the injection interval of anti-VEGF antibodies [64,76]. Moreover, this decrease is higher when the vitrectomy is performed in combination with a lensectomy. However, these results come from animal studies and their translation to humans is still controversial, which is mainly due to the anatomic and physiological differences between the species [76].

3.3. Analytical Methods Used in Pharmacokinetic Studies

The assessment of pharmacokinetic parameters for a drug administered by intravitreal route poses a challenge. It is not easy to obtain periodic samples of vitreous or aqueous fluids due to the invasive nature of the method. Moreover, when trying to assess drug systemic levels, the exposure may be low,

or the technique does not offer the sensitivity that is required to enable pharmacokinetic evaluations of antibodies. Most of the reported assays are based on ELISA (Enzyme-Linked ImmunoSorbent Assay) assays, which are considered the "gold standard" method used for the measurement of monoclonal antibodies [22,30,34]. Although there are a large variety of ELISA methods available for anti-VEGF antibodies determination, most of the work in this field relies on an indirect determination by VEGF, where factors, such as the type of VEGF, or the binding affinity, might have a big influence. Out of the three, ranibizumab is the one that requires a higher sensitivity and a more specific detection method, since the ranibizumab serum levels are often lower than the levels that can be detected by conventional methods [21,30]. The pharmacokinetic profile of Fab antibodies (such as ranibizumab) is characterised by a long elimination of the vitreous half-life and a rapid elimination from the systemic circulation [80]. Molecules containing a Fc region, such as bevacizumab or aflibercept, have greater systemic half-lives [58], because they are protected from proteolytic catabolism by binding to the neonatal Fc receptor (FcRn). However, the impact of FcRn receptor on the intravitreal pharmacokinetics is still unclear [70]. Additionally, high sensitivity ELISA methods require for drug samples to be diluted within the detection range, which can add some inaccuracy.

Lowe et al. developed a novel electrochemiluminescence assay (ECLA) that allowed for a more sensitive determination of ranibizumab in serum. This assay was first used to support some clinical trials, offering 67 times more sensitivity than a conventional ELISA (20 ng/mL) [81] and with a reporting range of 0.3–24 ng/mL [82]. More recently, the same authors have presented another novel method that utilises a high-affinity monoclonal anti-ranibizumab-VEGF-complexes antibody (MARA) to measure ranibizumab in human serum. The assay format uses a semi-homogeneous solution that specifically binds to the ranibizumab-VEGF complex, but neither one alone. This new ELISA method has a lower limit of quantification of 15 pg/mL in human serum [83].

There are still a few studies have attempted to improve the detection method, even though most of the studies quantify the anti-VEGF drugs concentration by immunoassays. Dickmann et al. assessed the ability of fluorophotometry to measure the intravitreal pharmacokinetics of fluorescently-labelled ranibizumab in the rabbit and compared the results to those that were obtained using ELISA in previous publications, obtaining similar results [84].

Christoforidis et al. tried a different approach by labelling bevacizumab, ranibizumab, and aflibercept with a radionuclide, such as I-124, to evaluate the pharmacokinetics of the intravitreally injected anti-VEGF drugs by PET/CT [26,45,60]. The great advantage of this method in comparison to the traditional ones using ELISA is that the vitreous anti-VEGF antibodies levels can be controlled without needing to sacrifice the animals at determined time intervals or without taking invasive samples of the vitreous humour.

HPLC (High Performance Liquid Chromatography) is a fast and low-cost quantification method, however it is not commonly used in antibodies determinations in biological samples. Giannos et al. tried to correlate ELISA analytical methods to SE-HPLC (size exclusion high performance liquid chromatography) on in vitro studies, showing a close and significant correlation between them. Their SE-HLPC method uses a new marketed column designed for antibodies with a lower limit of detection (LOD) of 2.19 ng/mL and a lower limit of quantification (LLQ) of 8.79 ng/mL for bevacizumab and ranibizumab. Aflibercept LOD and LLQ were 8.79 and 17.578 ng/mL, respectively [85]. No in vivo studies were found that used HPLC as an analytical method for anti-VEGF drugs.

4. Outlooks

All of the pharmacokinetic studies centre their reports on the half-lives of the anti-VEGF drugs in different compartments (vitreous, aqueous humour, or serum) (Figure 1). Their objective is to explain the route of elimination of the drug from the eye, in the case of animal studies, or to relate the findings to possible adverse drug effects when entering the systemic circulation.

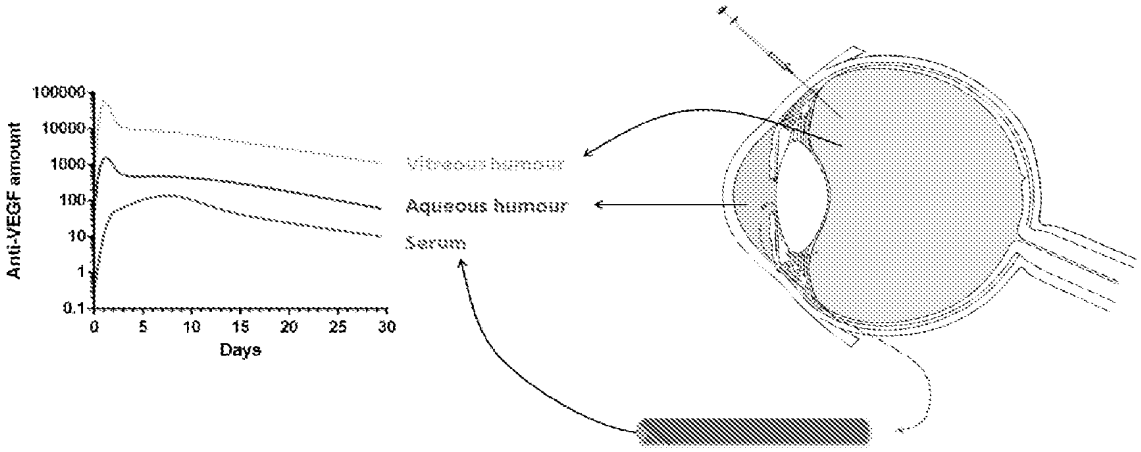


Figure 1. Scheme of the pharmacokinetic profiles after anti-VEGF antibodies intravitreal injection.

Only one study has compared the pharmacokinetics of the three anti-VEGF antibodies that were used in clinical practice [19]. Avery et al. compared the systemic exposure and the suppression of VEGF in plasma. Ranibizumab showed the least systemic exposure, whereas bevacizumab presented the highest with a 35-fold increase in AUC as compared to ranibizumab. These differences further increase after the third dose. Aflibercept appears to have the greatest suppression of free plasma VEGF out of the three, with serum concentrations that exceed its IC50 value (0.068 nM) at three hours post-injection and remain above this for seven days. In contrast, ranibizumab mean trough levels remained similar to the baseline [19].

However, no study has extensively examined the ocular pharmacokinetics of anti-VEGF antibodies in humans and their relation to the frequency of intravitreal doses. The establishment of the actual dosage regimens is mainly based on the activity of the disease that is assessed by OCT imaging or visual acuity and not on the pharmacokinetics of the drugs. An in vitro model in aqueous humour tried to associate the VEGF-A suppression times with the administration times, which suggested that individual dosing strategies are possible with a range of suppression of 26 to 69 days [86,87]. In humans, only one study determined levels of unbound aflibercept in a case series with seven patients that were treated over a six-month period with aflibercept and unbound VEGF-A in aqueous humour remained stable after every month and second month of intravitreal injections, supporting that bimonthly administrations may be enough in those patients that were treated with aflibercept [88].

Population pharmacokinetic analysis allows for the drug time-course profiles and the response dynamics over time to be characterised in a more precise manner. It also allows for the identification of the intrinsic and extrinsic factors that might be related to the observed drug exposure or response [86]. Population analysis, which is also known as non-linear mixed effects modelling, considers the structural pharmacokinetic or pharmacokinetic/pharmacodynamic models and stochastic models in order to account for inter-individual and/or inter-occasion variability and residual unexplained error [89–92]. Regulatory authorities have actually acknowledged the relevance of this discipline for drug approval and its value for an optimal dose selection in the special subgroups of the population [93,94]. However, these models are not used in the development of new agents for AMD, and only one author has applied the concepts of non-linear mixed effects modelling for the characterisation of the pharmacokinetic time-course profile of ranibizumab in this disease [22].

5. Conclusions

At present, the available pharmacokinetic data on anti-VEGF drugs after intravitreal administration are still limited, despite the fact that these molecules are the standard treatment for AMD. In recent years, many studies have been carried out in order to determine the main pharmacokinetic parameters of anti-VEGF antibodies in different animal species and humans, although the differences in the

methods of determination, in the samples analysed, in the time points taken, and the compartmental analysis, etc., make it difficult to attain standardised values for each anti-VEGF antibody. We believe that this comprehensive review will be of great use to research groups working on the pharmacokinetics of intravitreally administered VEGF inhibitors, although further studies are necessary in order to improve the knowledge in this area.

Funding: This work was partially supported by the ISCIII (PI17/00940, RETICS Oftared, RD16/0008/0003 and RD12/0034/0017) cofunded by FEDER and by the Spanish Ministry of Science, Innovation and Universities (RTI2018-099597-B-100).

Acknowledgments: A.L.-R. acknowledges the financial support of the Xunta de Galicia and the European Union (European Social Fund ESF) (predoctoral research fellowship). A.F.-F. and C.M.-G. acknowledge the support obtained from the Instituto de Salud Carlos III (ISCIII) through its research grants (JR18/00014 and CM18/00090). P.A. acknowledges "Ramón y Cajal" research fellowship (RYC-2015/17430).

Conflicts of Interest: The authors declare that there is no conflict of interest.

References

1. Pascolini, D.; Mariotti, S.P. Global estimates of visual impairment: 2010. *Br. J. Ophthalmol.* **2012**, *96*, 614–618. [CrossRef] [PubMed]
2. Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.G.; Klein, R.; Cheng, C.-Y.; Wong, T.Y. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *Lancet Glob. Health* **2014**, *2*, e106–e116. [CrossRef]
3. Ferris, F.L.; Wilkinson, C.P.; Bird, A.; Chakravarthy, U.; Chew, E.; Csaky, K.; Sadda, S.R. Beckman Initiative for Macular Research Classification Committee Clinical classification of age-related macular degeneration. *Ophthalmology* **2013**, *120*, 844–851. [CrossRef] [PubMed]
4. De Jong, P.T.V.M. Age-related macular degeneration. *N. Engl. J. Med.* **2006**, *355*, 1474–1485. [CrossRef] [PubMed]
5. Rohrer, B.; Frazer-Abel, A.; Leonard, A.; Ratnapriya, R.; Ward, T.; Pietraszkiewicz, A.; O'Quinn, E.; Adams, K.; Swaroop, A.; Wolf, B.J. Association of age-related macular degeneration with complement activation products, smoking, and single nucleotide polymorphisms in South Carolinians of European and African descent. *Mol. Vis.* **2019**, *25*, 79–92. [PubMed]
6. Empeslidis, T.; Storey, M.; Giannopoulos, T.; Konidaris, V.; Tranos, P.G.; Panagiotou, E.S.; Voudouragkaki, I.C.; Konstas, A.G. How Successful is Switching from Bevacizumab or Ranibizumab to Aflibercept in Age-Related Macular Degeneration? A Systematic Overview. *Adv. Ther.* **2019**, *36*, 1532–1548. [CrossRef] [PubMed]
7. Pershing, S.; Talwar, N.; Armenti, S.T.; Grubbs, J.; Rosenthal, J.M.; Dedania, V.S.; Stein, J.D. Use of Bevacizumab and Ranibizumab for Wet Age-Related Macular Degeneration: Influence of CATT Results and Introduction of Aflibercept. *Am. J. Ophthalmol.* **2019**. [CrossRef]
8. Cioffi, C.L.; Johnson, G.; Petrukhin, K. Recent Developments in Agents for the Treatment of Age-related Macular Degeneration and Stargardt Disease. In *2016 Medicinal Chemistry Reviews*; Desai, M.C., Ed.; MEDI Inc.: Baltimore, MA, USA, 2016; Volume 51, pp. 261–281. ISBN 978-0-9962932-3-5.
9. Neumann, R.; Barequet, D. The gap between the need for novel retinal drug delivery methods, technologies in R&D phase, and approved ocular drug delivery technologies. *Drug Discov. Today* **2019**. [CrossRef]
10. Brown, D.M.; Michels, M.; Kaiser, P.K.; Heier, J.S.; Sy, J.P.; Ianchulev, T. ANCHOR Study Group Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* **2009**, *116*, 57–65.e5. [CrossRef]
11. Rosenfeld, P.J.; Brown, D.M.; Heier, J.S.; Boyer, D.S.; Kaiser, P.K.; Chung, C.Y.; Kim, R.Y. MARINA Study Group Ranibizumab for neovascular age-related macular degeneration. *N. Engl. J. Med.* **2006**, *355*, 1419–1431. [CrossRef]
12. Heier, J.S.; Brown, D.M.; Chong, V.; Korobelnik, J.-F.; Kaiser, P.K.; Nguyen, Q.D.; Kirchhof, B.; Ho, A.; Ogura, Y.; Yancopoulos, G.D.; et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* **2012**, *119*, 2537–2548. [CrossRef] [PubMed]
13. Schmidt-Erfurth, U.; Garcia-Arumi, J.; Bandello, F.; Berg, K.; Chakravarthy, U.; Gerendas, B.S.; Jonas, J.; Larsen, M.; Tadayoni, R.; Loewenstein, A. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). *OPH* **2017**, *237*, 185–222. [CrossRef] [PubMed]

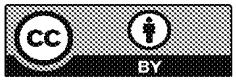
14. García-Layana, A.; Figueroa, M.S.; Arias, L.; Araiz, J.; Ruiz-Moreno, J.M.; García-Arumí, J.; Gómez-Ulla, F.; López-Gálvez, M.I.; Cabrera-López, F.; García-Campos, J.M.; et al. Individualized Therapy with Ranibizumab in Wet Age-Related Macular Degeneration. *J. Ophthalmol.* **2015**, *2015*, 412903. [CrossRef] [PubMed]
15. Cost comparison table of anti-VEGF therapies for W-AMD. In *Aflibercept (Eylea): Treatment of Neovascular (Wet) Age-Related Macular Degeneration (wAMD)*; CADTH Common Drug Reviews; Canadian Agency for Drugs and Technologies in Health: Ottawa, ON, Canada, 2015.
16. Okada, M.; Kandasamy, R.; Chong, E.W.; McGuiness, M.; Guymer, R.H. The Treat-and-Extend Injection Regimen Versus Alternate Dosing Strategies in Age-related Macular Degeneration: A Systematic Review and Meta-analysis. *Am. J. Ophthalmol.* **2018**, *192*, 184–197. [CrossRef] [PubMed]
17. Haga, A.; Kawaji, T.; Ideta, R.; Inomata, Y.; Tanihara, H. Treat-and-extend versus every-other-month regimens with aflibercept in age-related macular degeneration. *Acta Ophthalmol.* **2018**, *96*, e393–e398. [CrossRef] [PubMed]
18. Al-Zamil, W.M.; Yassin, S.A. Recent developments in age-related macular degeneration: A review. *Clin. Interv. Aging* **2017**, *12*, 1313–1330. [CrossRef]
19. Avery, R.L.; Castellarin, A.A.; Steinle, N.C.; Dhoot, D.S.; Pieramici, D.J.; See, R.; Couvillion, S.; Nasir, M.A.; Rabena, M.D.; Le, K.; et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. *Br. J. Ophthalmol.* **2014**, *98*, 1636–1641. [CrossRef]
20. Bhagat, R.; Zhang, J.; Farooq, S.; Li, X.-Y. Comparison of the release profile and pharmacokinetics of intact and fragmented dexamethasone intravitreal implants in rabbit eyes. *J. Ocul. Pharmacol. Ther.* **2014**, *30*, 854–858. [CrossRef]
21. Bakri, S.J.; Snyder, M.R.; Reid, J.M.; Pulido, J.S.; Ezzat, M.K.; Singh, R.J. Pharmacokinetics of intravitreal ranibizumab (Lucentis). *Ophthalmology* **2007**, *114*, 2179–2182. [CrossRef]
22. Xu, L.; Lu, T.; Tuomi, L.; Jumbe, N.; Lu, J.; Eppler, S.; Kuebler, P.; Damico-Beyer, L.A.; Joshi, A. Pharmacokinetics of ranibizumab in patients with neovascular age-related macular degeneration: A population approach. *Investig. Ophthalmol. Vis. Sci.* **2013**, *54*, 1616–1624. [CrossRef]
23. Papadopoulos, N.; Martin, J.; Ruan, Q.; Rafique, A.; Rosconi, M.P.; Shi, E.; Pyles, E.A.; Yancopoulos, G.D.; Stahl, N.; Wiegand, S.J. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* **2012**, *15*, 171–185. [CrossRef] [PubMed]
24. Li, S.K.; Liddell, M.R.; Wen, H. Effective electrophoretic mobilities and charges of anti-VEGF proteins determined by capillary zone electrophoresis. *J. Pharm. Biomed. Anal.* **2011**, *55*, 603–607. [CrossRef] [PubMed]
25. Holash, J.; Davis, S.; Papadopoulos, N.; Croll, S.D.; Ho, L.; Russell, M.; Boland, P.; Leidich, R.; Hylton, D.; Burova, E.; et al. VEGF-Trap: A VEGF blocker with potent antitumor effects. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11393–11398. [CrossRef] [PubMed]
26. Christoforidis, J.B.; Carlton, M.M.; Knopp, M.V.; Hinkle, G.H. PET/CT imaging of I-124-radiolabeled bevacizumab and ranibizumab after intravitreal injection in a rabbit model. *Investig. Ophthalmol. Vis. Sci.* **2011**, *52*, 5899–5903. [CrossRef] [PubMed]
27. Ahn, S.J.; Ahn, J.; Park, S.; Kim, H.; Hwang, D.J.; Park, J.H.; Park, J.Y.; Chung, J.Y.; Park, K.H.; Woo, S.J. Intraocular pharmacokinetics of ranibizumab in vitrectomized versus nonvitrectomized eyes. *Investig. Ophthalmol. Vis. Sci.* **2014**, *55*, 567–573. [CrossRef] [PubMed]
28. Gaudreault, J.; Fei, D.; Beyer, J.C.; Ryan, A.; Rangell, L.; Shiu, V.; Damico, L.A. Pharmacokinetics and retinal distribution of ranibizumab, a humanized antibody fragment directed against VEGF-A, following intravitreal administration in rabbits. *Retina* **2007**, *27*, 1260–1266. [CrossRef] [PubMed]
29. Christoforidis, J.B.; Briley, K.; Binzel, K.; Bhatia, P.; Wei, L.; Kumar, K.; Knopp, M.V. Systemic Biodistribution and Intravitreal Pharmacokinetic Properties of Bevacizumab, Ranibizumab, and Aflibercept in a Nonhuman Primate Model. *Investig. Ophthalmol. Vis. Sci.* **2017**, *58*, 5636–5645. [CrossRef] [PubMed]
30. Gaudreault, J.; Fei, D.; Rusit, J.; Suboc, P.; Shiu, V. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. *Investig. Ophthalmol. Vis. Sci.* **2005**, *46*, 726–733. [CrossRef] [PubMed]
31. Avery, R.L.; Castellarin, A.A.; Steinle, N.C.; Dhoot, D.S.; Pieramici, D.J.; See, R.; Couvillion, S.; Nasir, M.A.; Rabena, M.D.; Maia, M.; et al. Systemic pharmacokinetics and pharmacodynamics of intravitreal aflibercept, bevacizumab, and ranibizumab. *Retina* **2017**, *37*, 1847–1858. [CrossRef]

32. Krohne, T.U.; Liu, Z.; Holz, F.G.; Meyer, C.H. Intraocular pharmacokinetics of ranibizumab following a single intravitreal injection in humans. *Am. J. Ophthalmol.* **2012**, *154*, 682–686. [CrossRef] [PubMed]
33. Stewart, M.W. What are the half-lives of ranibizumab and aflibercept (VEGF Trap-eye) in human eyes? Calculations with a mathematical model. *Eye Rep.* **2011**, *1*, 5. [CrossRef]
34. Moisseiev, E.; Waisbourd, M.; Ben-Artsi, E.; Levinger, E.; Barak, A.; Daniels, T.; Csaky, K.; Loewenstein, A.; Barequet, I.S. Pharmacokinetics of bevacizumab after topical and intravitreal administration in human eyes. *Graefes Arch. Clin. Exp. Ophthalmol.* **2014**, *252*, 331–337. [CrossRef] [PubMed]
35. Tew, W.P.; Gordon, M.; Murren, J.; Dupont, J.; Pezzulli, S.; Aghajanian, C.; Sabbatini, P.; Mendelson, D.; Schwartz, L.; Gettinger, S.; et al. Phase 1 study of aflibercept administered subcutaneously to patients with advanced solid tumors. *Clin. Cancer Res.* **2010**, *16*, 358–366. [CrossRef] [PubMed]
36. Wang, X.; Sawada, T.; Sawada, O.; Saishin, Y.; Liu, P.; Ohji, M. Serum and plasma vascular endothelial growth factor concentrations before and after intravitreal injection of aflibercept or ranibizumab for age-related macular degeneration. *Am. J. Ophthalmol.* **2014**, *158*, 738–744. [CrossRef] [PubMed]
37. Zehetner, C.; Kirchmair, R.; Huber, S.; Kralinger, M.T.; Kieselbach, G.F. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. *Br. J. Ophthalmol* **2013**, *97*, 454–459. [CrossRef] [PubMed]
38. Zehetner, C.; Kralinger, M.T.; Modi, Y.S.; Waltl, I.; Ulmer, H.; Kirchmair, R.; Bechrakis, N.E.; Kieselbach, G.F. Systemic levels of vascular endothelial growth factor before and after intravitreal injection of aflibercept or ranibizumab in patients with age-related macular degeneration: A randomised, prospective trial. *Acta Ophthalmol.* **2015**, *93*, e154–e159. [CrossRef] [PubMed]
39. Reimbursement by a National Healthcare Insurance System of a Medicinal Product for a Use Not Covered by Its Marketing Authorisation (Off-Label Use). Available online: http://curia.europa.eu/juris/document/document.jsf?text=&docid=207947&pageIndex=0&doclang=en&mode=req&dir=&occ=first&part=1 (accessed on 29 May 2019).
40. Dakin, H.A.; Wordsworth, S.; Rogers, C.A.; Abangma, G.; Raftery, J.; Harding, S.P.; Lotery, A.J.; Downes, S.M.; Chakravarthy, U.; Reeves, B.C.; et al. Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial. *BMJ Open* **2014**, *4*, e005094. [CrossRef] [PubMed]
41. Bakri, S.J.; Snyder, M.R.; Reid, J.M.; Pulido, J.S.; Singh, R.J. Pharmacokinetics of intravitreal bevacizumab (Avastin). *Ophthalmology* **2007**, *114*, 855–859. [CrossRef]
42. Nomoto, H.; Shiraga, F.; Kuno, N.; Kimura, E.; Fujii, S.; Shinomiya, K.; Nugent, A.K.; Hirooka, K.; Baba, T. Pharmacokinetics of bevacizumab after topical, subconjunctival, and intravitreal administration in rabbits. *Investig. Ophthalmol. Vis. Sci.* **2009**, *50*, 4807–4813. [CrossRef]
43. Sinapis, C.I.; Routsias, J.G.; Sinapis, A.I.; Sinapis, D.I.; Agrogiannis, G.D.; Pantopoulou, A.; Theocharis, S.E.; Baltatzis, S.; Patsouris, E.; Perrea, D. Pharmacokinetics of intravitreal bevacizumab (Avastin®) in rabbits. *Clin. Ophthalmol* **2011**, *5*, 697–704. [CrossRef]
44. Miyake, T.; Sawada, O.; Kakinoki, M.; Sawada, T.; Kawamura, H.; Ogasawara, K.; Ohji, M. Pharmacokinetics of bevacizumab and its effect on vascular endothelial growth factor after intravitreal injection of bevacizumab in macaque eyes. *Investig. Ophthalmol. Vis. Sci.* **2010**, *51*, 1606–1608. [CrossRef] [PubMed]
45. Christoforidis, J.B.; Williams, M.M.; Kothandaraman, S.; Kumar, K.; Epitropoulos, F.J.; Knopp, M.V. Pharmacokinetic properties of intravitreal I-124-aflibercept in a rabbit model using PET/CT. *Curr. Eye Res.* **2012**, *37*, 1171–1174. [CrossRef] [PubMed]
46. Dınc, E.; Yıldırım, O.; Necat Yılmaz, S.; Canacankatan, N.; Ayaz, L.; Ozcan, T.; Temel, G.O. Intravitreal bevacizumab effects on VEGF levels in distant organs: An experimental study. *Cutan. Ocul. Toxicol.* **2014**, *33*, 275–282. [CrossRef] [PubMed]
47. Zhu, Q.; Ziemssen, F.; Henke-Fahle, S.; Tatar, O.; Szurman, P.; Aisenbrey, S.; Schneiderhan-Marra, N.; Xu, X. Tübingen Bevacizumab Study Group; Grisanti, S. Vitreous levels of bevacizumab and vascular endothelial growth factor-A in patients with choroidal neovascularization. *Ophthalmology* **2008**, *115*, 1750–1755. [CrossRef] [PubMed]
48. Yu, L.; Liang, X.H.; Ferrara, N. Comparing protein VEGF inhibitors: In vitro biological studies. *Biochem. Biophys. Res. Commun.* **2011**, *408*, 276–281. [CrossRef] [PubMed]

49. Dedania, V.S.; Bakri, S.J. Systemic safety of intravitreal anti-vascular endothelial growth factor agents in age-related macular degeneration. *Curr. Opin. Ophthalmol.* **2016**, *27*, 224–243. [CrossRef] [PubMed]
50. Moja, L.; Lucenteforte, E.; Kwag, K.H.; Bertele, V.; Campomori, A.; Chakravarthy, U.; D'Amico, R.; Dickersin, K.; Kodjikian, L.; Lindsley, K.; et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. *Cochrane Database Syst. Rev.* **2014**, CD011230. [CrossRef]
51. Thulliez, M.; Angoulvant, D.; Le Lez, M.L.; Jonville-Bera, A.-P.; Pisella, P.-J.; Gueyffier, F.; Bejan-Angoulvant, T. Cardiovascular events and bleeding risk associated with intravitreal antivascular endothelial growth factor monoclonal antibodies: Systematic review and meta-analysis. *JAMA Ophthalmol.* **2014**, *132*, 1317–1326. [CrossRef] [PubMed]
52. Krohne, T.U.; Eter, N.; Holz, F.G.; Meyer, C.H. Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans. *Am. J. Ophthalmol.* **2008**, *146*, 508–512. [CrossRef] [PubMed]
53. Meyer, C.H.; Krohne, T.U.; Holz, F.G. Intraocular pharmacokinetics after a single intravitreal injection of 1.5 mg versus 3.0 mg of bevacizumab in humans. *Retina* **2011**, *31*, 1877–1884. [CrossRef] [PubMed]
54. Meyer, C.H.; Krohne, T.U.; Holz, F.G. Concentrations of unbound bevacizumab in the aqueous of untreated fellow eyes after a single intravitreal injection in humans. *Acta Ophthalmol.* **2012**, *90*, 68–70. [CrossRef]
55. Park, S.J.; Choi, Y.; Na, Y.M.; Hong, H.K.; Park, J.Y.; Park, K.H.; Chung, J.Y.; Woo, S.J. Intraocular Pharmacokinetics of Intravitreal Aflibercept (Eylea) in a Rabbit Model. *Investig. Ophthalmol. Vis. Sci.* **2016**, *57*, 2612–2617. [CrossRef] [PubMed]
56. Niwa, Y.; Kakinoki, M.; Sawada, T.; Wang, X.; Ohji, M. Ranibizumab and Aflibercept: Intraocular Pharmacokinetics and Their Effects on Aqueous VEGF Level in Vitrectomized and Nonvitrectomized Macaque Eyes. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 6501–6505. [CrossRef] [PubMed]
57. Kaiser, P.K.; Kodjikian, L.; Korobelnik, J.-F.; Winkler, J.; Torri, A.; Zeitz, O.; Vitti, R.; Ahlers, C.; Zimmermann, T.; Dicioccio, A.T.; et al. Systemic pharmacokinetic/pharmacodynamic analysis of intravitreal aflibercept injection in patients with retinal diseases. *BMJ. Open Ophthalmol.* **2019**, *4*, e000185. [CrossRef]
58. Stewart, M.W. Pharmacokinetics, pharmacodynamics and pre-clinical characteristics of ophthalmic drugs that bind VEGF. *Expert Rev. Clin. Pharmacol* **2014**, *7*, 167–180. [CrossRef] [PubMed]
59. Do, D.V.; Rhoades, W.; Nguyen, Q.D. Pharmacokinetic study of intravitreal aflibercept in humans with neovascular age-related macular degeneration. *Retina* **2019**. [CrossRef] [PubMed]
60. Christoforidis, J.B.; Williams, M.M.; Wang, J.; Jiang, A.; Pratt, C.; Abdel-Rasoul, M.; Hinkle, G.H.; Knopp, M.V. Anatomic and pharmacokinetic properties of intravitreal bevacizumab and ranibizumab after vitrectomy and lensectomy. *Retina* **2013**, *33*, 946–952. [CrossRef] [PubMed]
61. Christoforidis, J.B.; Xie, Z.; Jiang, A.; Wang, J.; Pratt, C.; Gemensky-Metzler, A.; Abdel-Rasoul, M.; Roy, S.; Liu, Z. Serum levels of intravitreal bevacizumab after vitrectomy, lensectomy and non-surgical controls. *Curr. Eye Res.* **2013**, *38*, 761–766. [CrossRef] [PubMed]
62. Ahn, J.; Kim, H.; Woo, S.J.; Park, J.H.; Park, S.; Hwang, D.J.; Park, K.H. Pharmacokinetics of intravitreally injected bevacizumab in vitrectomized eyes. *J. Ocul. Pharmacol. Ther.* **2013**, *29*, 612–618. [CrossRef] [PubMed]
63. Liu, X.; Ye, J.; Zhang, Y.; Liu, Q.; Bai, R.; Yuan, W.; Cai, D.; Zheng, X.; Bian, Y.; Zhou, S.; et al. Ocular Biodistribution of ^{89}Zr-Bevacizumab in New Zealand Rabbits Determined Using PET/MRI: A Feasibility Study. *Iran. J. Radiol.* **2019**, *16*. [CrossRef]
64. Kakinoki, M.; Sawada, O.; Sawada, T.; Saishin, Y.; Kawamura, H.; Ohji, M. Effect of vitrectomy on aqueous VEGF concentration and pharmacokinetics of bevacizumab in macaque monkeys. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 5877–5880. [CrossRef] [PubMed]
65. Missel, P.J. Simulating intravitreal injections in anatomically accurate models for rabbit, monkey, and human eyes. *Pharm. Res.* **2012**, *29*, 3251–3272. [CrossRef] [PubMed]
66. Xu, Q.; Boylan, N.J.; Suk, J.S.; Wang, Y.-Y.; Nance, E.A.; Yang, J.-C.; McDonnell, P.J.; Cone, R.A.; Duh, E.J.; Hanes, J. Nanoparticle diffusion in, and microrheology of, the bovine vitreous ex vivo. *J. Control Release* **2013**, *167*, 76–84. [CrossRef] [PubMed]
67. Laude, A.; Tan, L.E.; Wilson, C.G.; Lascaratos, G.; Elashry, M.; Aslam, T.; Patton, N.; Dhillon, B. Intravitreal therapy for neovascular age-related macular degeneration and inter-individual variations in vitreous pharmacokinetics. *Prog. Retin. Eye Res.* **2010**, *29*, 466–475. [CrossRef] [PubMed]
68. Angi, M.; Kalirai, H.; Coupland, S.E.; Damato, B.E.; Semeraro, F.; Romano, M.R. Proteomic analyses of the vitreous humour. *Mediat. Inflamm.* **2012**, *2012*, 148039. [CrossRef] [PubMed]

69. Ulrich, J.N.; Spannagl, M.; Kampik, A.; Gandorfer, A. Components of the fibrinolytic system in the vitreous body in patients with vitreoretinal disorders. *Clin. Experiment. Ophthalmol.* **2008**, *36*, 431–436. [CrossRef]
70. Del Amo, E.M.; Rimpelä, A.-K.; Heikkinen, E.; Kari, O.K.; Ramsay, E.; Lajunen, T.; Schmitt, M.; Pelkonen, L.; Bhattacharya, M.; Richardson, D.; et al. Pharmacokinetic aspects of retinal drug delivery. *Prog. Retin Eye Res.* **2017**, *57*, 134–185. [CrossRef]
71. Gal-Or, O.; Dotan, A.; Dachbash, M.; Tal, K.; Nisgav, Y.; Weinberger, D.; Ehrlich, R.; Livnat, T. Bevacizumab clearance through the iridocorneal angle following intravitreal injection in a rat model. *Exp. Eye Res.* **2016**, *145*, 412–416. [CrossRef]
72. Peters, S.; Heiduschka, P.; Julien, S.; Ziemssen, F.; Fietz, H.; Bartz-Schmidt, K.U. Tübingen Bevacizumab Study Group; Schraermeyer, U. Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab. *Am. J. Ophthalmol.* **2007**, *143*, 995–1002. [CrossRef]
73. Heiduschka, P.; Fietz, H.; Hofmeister, S.; Schultheiss, S.; Mack, A.F.; Peters, S.; Ziemssen, F.; Niggemann, B.; Julien, S.; Bartz-Schmidt, K.U.; et al. Penetration of bevacizumab through the retina after intravitreal injection in the monkey. *Investig. Ophthalmol. Vis. Sci.* **2007**, *48*, 2814–2823. [CrossRef]
74. Vellonen, K.-S.; Hellinen, L.; Mannermaa, E.; Ruponen, M.; Urtti, A.; Kidron, H. Expression, activity and pharmacokinetic impact of ocular transporters. *Adv. Drug Deliv. Rev.* **2018**, *126*, 3–22. [CrossRef] [PubMed]
75. Krohne, T.U.; Muether, P.S.; Stratmann, N.K.; Holz, F.G.; Kirchhof, B.; Meyer, C.H.; Fauser, S. Influence of ocular volume and lens status on pharmacokinetics and duration of action of intravitreal vascular endothelial growth factor inhibitors. *Retina* **2015**, *35*, 69–74. [CrossRef] [PubMed]
76. Edington, M.; Connolly, J.; Chong, N.V. Pharmacokinetics of intravitreal anti-VEGF drugs in vitrectomized versus non-vitrectomized eyes. *Expert Opin Drug Metab Toxicol* **2017**, *13*, 1217–1224. [CrossRef] [PubMed]
77. Gisladottir, S.; Loftsson, T.; Stefansson, E. Diffusion characteristics of vitreous humour and saline solution follow the Stokes Einstein equation. *Graefes Arch. Clin. Exp. Ophthalmol.* **2009**, *247*, 1677–1684. [CrossRef] [PubMed]
78. Stefánsson, E. Physiology of vitreous surgery. *Graefes Arch. Clin. Exp. Ophthalmol.* **2009**, *247*, 147–163. [CrossRef] [PubMed]
79. Xu, Y.; You, Y.; Du, W.; Zhao, C.; Li, J.; Mao, J.; Chen, H.; Cheng, L. Ocular pharmacokinetics of bevacizumab in vitrectomized eyes with silicone oil tamponade. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 5221–5226. [CrossRef] [PubMed]
80. Gadkar, K.; Pastuskovas, C.V.; Le Couter, J.E.; Elliott, J.M.; Zhang, J.; Lee, C.V.; Sanowar, S.; Fuh, G.; Kim, H.S.; Lombana, T.N.; et al. Design and Pharmacokinetic Characterization of Novel Antibody Formats for Ocular Therapeutics. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 5390–5400. [CrossRef] [PubMed]
81. Lowe, J.; Maia, M.; Wakshull, E.; Siguenza, P.; Liu, P.; Lakhani, S.; Rusit, J.; Elliott, R.; Quarmby, V. Development of a novel homogenous electrochemiluminescence assay for quantitation of ranibizumab in human serum. *J. Pharm. Biomed. Anal.* **2010**, *52*, 680–686. [CrossRef]
82. Zhang, Y.; Yao, Z.; Kaila, N.; Kuebler, P.; Visich, J.; Maia, M.; Tuomi, L.; Ehrlich, J.S.; Rubio, R.G.; Campochiaro, P.A. Pharmacokinetics of ranibizumab after intravitreal administration in patients with retinal vein occlusion or diabetic macular edema. *Ophthalmology* **2014**, *121*, 2237–2246. [CrossRef]
83. Lowe, J.; Wakshull, E.; Shek, T.; Chuntharapai, A.; Elliott, R.; Rusit, J.; Maia, M. Development and validation of a novel semi-homogenous clinical assay for quantitation of Ranibizumab in human serum. *J. Immunol. Methods* **2018**, *461*, 44–52. [CrossRef]
84. Dickmann, L.J.; Yip, V.; Li, C.; Abundes, J.; Maia, M.; Young, C.; Stainton, S.; Hass, P.E.; Joseph, S.B.; Prabhu, S.; et al. Evaluation of Fluorophotometry to Assess the Vitreal Pharmacokinetics of Protein Therapeutics. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 6991–6999. [CrossRef] [PubMed]
85. Giannos, S.A.; Kraft, E.R.; Zhao, Z.-Y.; Merkley, K.H.; Cai, J. Formulation Stabilization and Disaggregation of Bevacizumab, Ranibizumab and Aflibercept in Dilute Solutions. *Pharm. Res.* **2018**, *35*, 78. [CrossRef] [PubMed]
86. Muether, P.S.; Hermann, M.M.; Dröge, K.; Kirchhof, B.; Fauser, S. Long-term stability of vascular endothelial growth factor suppression time under ranibizumab treatment in age-related macular degeneration. *Am. J. Ophthalmol.* **2013**, *156*, 989–993. [CrossRef] [PubMed]
87. Saunders, D.J.; Muether, P.S.; Fauser, S. A model of the ocular pharmacokinetics involved in the therapy of neovascular age-related macular degeneration with ranibizumab. *Br. J. Ophthalmol.* **2015**, *99*, 1554–1559. [CrossRef] [PubMed]

88. Celik, N.; Scheuerle, A.; Auffarth, G.U.; Kopitz, J.; Dithmar, S. Intraocular Pharmacokinetics of Aflibercept and Vascular Endothelial Growth Factor-A. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 5574–5578. [CrossRef] [PubMed]
89. Mould, D.R.; Upton, R.N. Basic concepts in population modeling, simulation, and model-based drug development. *CPT Pharmacomet. Syst Pharmacol* **2012**, *1*, e6. [CrossRef] [PubMed]
90. Sheiner, L.B.; Rosenberg, B.; Melmon, K.L. Modelling of individual pharmacokinetics for computer-aided drug dosage. *Comput. Biomed. Res.* **1972**, *5*, 411–459. [CrossRef]
91. Sheiner, L.B.; Beal, S.L. Evaluation of methods for estimating population pharmacokinetics parameters. I. Michaelis-Menten model: Routine clinical pharmacokinetic data. *J. Pharmacokinet. Biopharm.* **1980**, *8*, 553–571. [CrossRef] [PubMed]
92. Stanski, D.R.; Maitre, P.O. Population pharmacokinetics and pharmacodynamics of thiopental: The effect of age revisited. *Anesthesiology* **1990**, *72*, 412–422. [CrossRef] [PubMed]
93. Manolis, E.; Brogren, J.; Cole, S.; Hay, J.L.; Nordmark, A.; Karlsson, K.E.; Lentz, F.; Benda, N.; Wangorsch, G.; Pons, G.; et al. Commentary on the MID3 Good Practices Paper. *CPT Pharmacomet. Syst. Pharmacol.* **2017**, *6*, 416–417. [CrossRef] [PubMed]
94. Marshall, S.; Burghaus, R.; Cosson, V.; Cheung, S.; Chenel, M.; DellaPasqua, O.; Frey, N.; Hamrén, B.; Harnisch, L.; Ivanow, F.; et al. Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation. *CPT Pharmacomet. Syst. Pharmacol.* **2016**, *5*, 93–122.



VEGF Trap induces antiglioma effect at different stages of disease

Candelaria Gomez-Manzano, Jocelyn Holash, Juan Fueyo, Jing Xu, Charles A. Conrad, Kenneth D. Aldape, John F. de Groot, B. Nebiyou Bekele, and W. K. Alfred Yung

Departments of Neuro-Oncology (C.G.-M., J.F., J.X., C.A.C., J.F.G., W.K.A.Y.), Pathology (K.D.A.), and Biostatistics and Applied Mathematics (B.N.B.), The University of Texas M. D. Anderson Cancer Center, Houston, TX; Regeneron Pharmaceuticals, Inc., Tarrytown, NY (J.H.); USA

Pathological angiogenesis is a hallmark of cancer, specifically of glioblastomas, the most malignant and common primary brain tumor. Vascular endothelial growth factor (VEGF) is the key protein in the regulation of the hypervascular phenotype of primary malignant brain tumors. In this study, we tested VEGF Trap, a soluble decoy receptor for VEGF, in an intracranial glioma model. VEGF Trap was administered in short or prolonged schedules to animals bearing human gliomas at different stages of disease. Of importance, VEGF Trap treatment was efficacious in both initial and advanced phases of tumor development by significantly increasing overall survival. Furthermore, this effect was enhanced in animals treated with more prolonged regimens. In addition, we observed the emergence of a VEGF Trap-resistant phenotype characterized by tumor growth and increased invasiveness. Our results suggest that VEGF Trap will be effective in treating both patients with recurrent or progressive resectable glioblastoma and patients that have undergone extensive initial surgery. Finally, our results indicate that the clinical success of VEGF Trap may depend on a prolonged treatment in combined therapy aiming to simultaneously inhibit angiogenesis and tumor invasion. *Neuro-Oncology 10, 940–945, 2008 (Posted to Neuro-Oncology [serial online], Doc. D08-00085, August 14, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-061)*

Received April 7, 2008; accepted June 4, 2008.

Address correspondence to C. Gomez-Manzano, Department of Neuro-Oncology, Unit 1002, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA (cmanzano@mdanderson.org).

Keywords: glioblastoma, therapy, VEGF, VEGF Trap

The striking induction of angiogenesis in glioblastoma multiforme (GBM) has fueled the speculation that progression to GBM requires the activation of angiogenesis, a finding that has stimulated significant efforts to develop angiogenesis-blocking agents. Vascular endothelial growth factor (VEGF) is critical for promoting the earliest stages of vasculogenesis, which includes endothelial cell proliferation, differentiation, migration, and tubular formation. Clinical trials of specific VEGF inhibitors for the treatment of patients with gliomas are ongoing, and preliminary analyses showed beneficial effects in patients with malignant gliomas.[1–4] Recently, a new anti-VEGF agent, VEGF Trap/aflibercept (henceforth referred to as VEGF Trap), has been developed by incorporating domains of both VEGF receptor 1 (VEGFR-1) and VEGFR-2 fused to the constant region of human immunoglobulin G1, which acts as a soluble decoy receptor for VEGF. VEGF Trap has very high affinity for all isoforms of VEGF-A (<1 pM), as well as placental growth factor, a closely related angiogenic factor.[5] VEGF Trap was engineered to have minimal interactions with the extracellular matrix, and this property apparently accounts for its satisfying pharmacokinetic profile superior to soluble forms of VEGFR-1.[5] Its efficacy has been proven in preclinical studies in several types of solid tumor[5–9] and in a subcutaneous glioma model.[10] Because tumor progression and angiogenesis are greatly dependent on the existent microenvironment of the tumor,[11,12] we undertook this study to characterize the effect of VEGF Trap in an orthotopic glioblastoma model in several stages of the disease. We

have previously described the development of growth patterns and angiogenesis in an intracranial U-87 MG human glioma model. Vessel cooption and remodeling were present at the early stages of disease, whereas the advanced stages are distinguished by high vascular density.[13] These two phases were similar to stages described in other previous reports.[14,15] Based on this tumoral angiogenesis and kinetic pattern, we administered VEGF Trap to animals bearing U-87 MG intracranial xenografts at several phases of tumor development. In the present study, we demonstrated that VEGF Trap treatment in animals bearing human gliomas resulted in significant prolonged survival. Of importance, our results indicate that VEGF Trap was equally effective against initial or advanced disease, and that the response was enhanced when VEGF Trap was administered in a prolonged schedule.

Material and Methods

Cell Line

The human glioma cell line U-87 MG was purchased from the American Type Culture Collection (Manassas, VA, USA). Cells were maintained in Dulbecco's modified Eagle/F12 medium (1:1, vol:vol) (The University of Texas M. D. Anderson Cancer Center Media Core Facility, Houston, TX, USA) supplemented with 10% fetal calf serum and 1% antibiotic/antimycotic agent (Invitrogen, Carlsbad, CA, USA) in a humidified atmosphere containing 5% CO_2 at 37°C.

Drugs

VEGF Trap and human Fc (hFc, constant region of human IgG1) were kindly provided by Regeneron Pharmaceuticals (Tarrytown, NY, USA). Stocks of 50 mg/ml in aqueous solution were kept at −80°C.

In Vivo Experiments

The U-87 MG human glioma cells (5×10^5) were engrafted in the caudate nucleus of athymic mice (Harlan Sprague Dawley Inc., Indianapolis, IN, USA), as previously described.[13] At 0, 4, and 10 days after cell implantation, we administered VEGF Trap (25 mg/kg subcutaneously, twice a week, for a total of 3 or 6 weeks) to separate groups of 10–15 animals per treatment bearing U-87 MG intracranial xenografts. Either phosphate-buffered saline (PBS) or hFc was blindly administered as a control agent in randomly selected subgroups of glioma-bearing animals. Animals showing generalized or local symptoms of disease were euthanized. Brains were fixed in 4% formaldehyde for 24 h and embedded in paraffin. Slides were stained with hematoxylin and eosin. All animal studies were performed in the veterinary facilities of The M. D. Anderson Cancer Center in accordance with institutional guidelines.

Enzyme-Linked Immunosorbent Assays

Blood was collected from the tail vein of glioma-bearing mice 3 days after the initial dose of VEGF Trap, hFc, or vehicle, and VEGF Trap was quantified in the serum by enzyme-linked immunosorbent assays (ELISA), as previously reported.[16]

Statistical Analyses

The in vivo anticancer effect of different treatments was assessed by plotting Kaplan-Meier survival curves, and treatment groups were compared using the log-rank test. The effects of VEGF Trap when administered in different treatment schedules were analyzed using a permutation test.

Results and Discussion

Antiglioma Effect of VEGF Trap on Initial Disease

The VEGF Trap-mediated antiglioma effect was assessed in vivo using an intracranial human glioma xenograft model. We selected the U-87 MG cell line for this study because it produces gliomas in nude mice with highly predictable growth kinetics and well-characterized pathological features[13]; in addition, U-87 MG cells express high levels of VEGF and, when implanted intracranially in immunocompromised mice, develop as highly vascularized tumors.[11,13] Our group has previously characterized the kinetics of tumor growth and vascularization of human U-87 MG xenografts implanted intracranially in nude mice. Of interest to the present study, U-87 MG intracranial tumors exhibited initially minimal tumor growth, but changes in the host vessels were evident as soon as day 1 and definitely by day 4 after implantation; these changes included significant vessel co-option, as illustrated by the existence of engorged smooth-muscle actin (SMA)-positive vascular structures in the periphery of the xenograft.[13]

To test the effect of VEGF Trap in the initial phases of the disease, we planned two different treatment schedules (Figs. 1 and 2) consisting of the subcutaneous administration of 25 mg/kg VEGF Trap twice weekly over 3 weeks, starting on either day 0 (schedule A) or day 4 (schedule B) after the intracranial implantation of human glioma cells in nude mice. Control groups were treated with PBS or hFc at doses and volumes similar to those used for the test drug. The agents were administered in a double-blinded manner; that is, the identity of the test groups was concealed from both the personnel preparing the drugs and the animal caretakers.

Animals treated with VEGF Trap starting on day 0 or day 4 after implantation had significantly prolonged survival compared to the hFc- or PBS-treated animals ($p < 0.0001$ and $p < 0.005$, respectively). In animals treated with schedule A, the median overall survival of the control-treated animals (treated with either hFc or PBS) was 30 days, with all animals dying by day 33. Treatment with VEGF Trap prolonged the mean survival

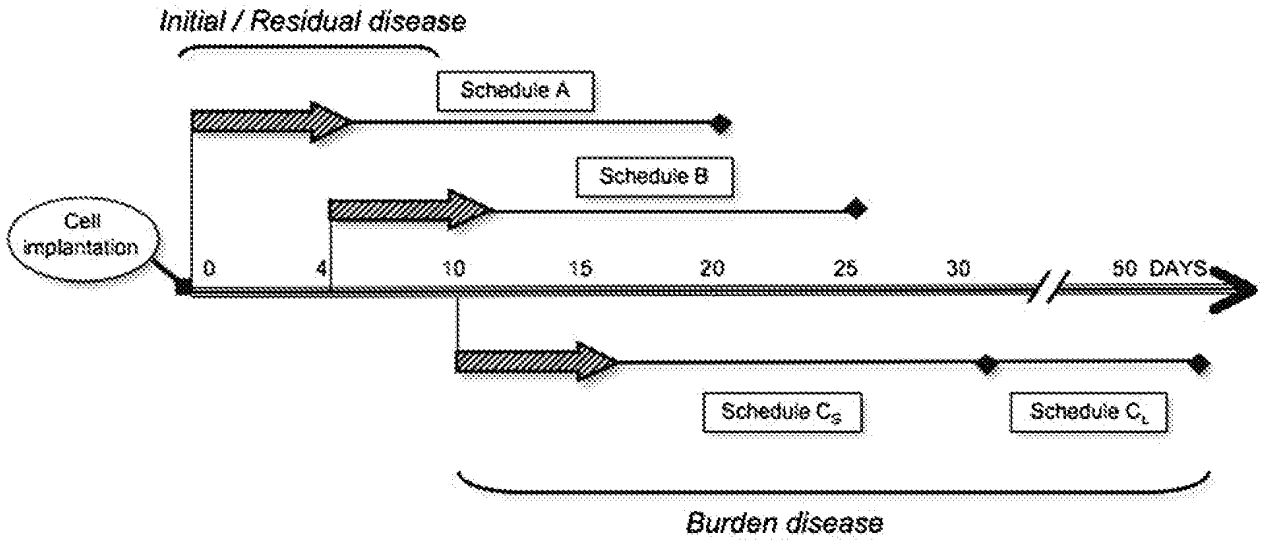


Fig. 1. Schematic representation of the treatment schedule used with the anti-vascular endothelial growth factor (VEGF) agent VEGF Trap, which was based on our previous studies of the kinetics of growth and vascularization in the U-87 MG intracranial model. U-87 MG cells were implanted in the brains of the animals on day 0, and VEGF Trap was administered starting on day 0 (schedule A), day 4 (schedule B), or day 10 (schedules C_S and C_L) after cell implantation. The two schedule C subgroups were treated in either a 3-week (schedule C_S) or 6-week (schedule C_L) schedule. Schedules A and B followed a 3-week treatment regimen. Animals were euthanized when signs of neurological or generalized disease appeared.

by 8 days. In animals treated with schedule B, the mean survival in the PBS- and hFc-treated animals was 27.5 and 30 days, respectively, but it was increased to 36 days in the group treated with VEGF Trap. No treatment-schedule-dependent differences in survival duration were observed in animals receiving VEGF Trap, suggesting VEGF Trap is efficacious in initial phases of disease that were characterized by active vessel co-option and remodeling. Analysis performed 3 days after the first VEGF Trap doses were administered revealed high VEGF Trap levels (approximately >50 μg/ml) in the serum of all these animals, suggesting an efficient systemic biodistribution (data not shown).

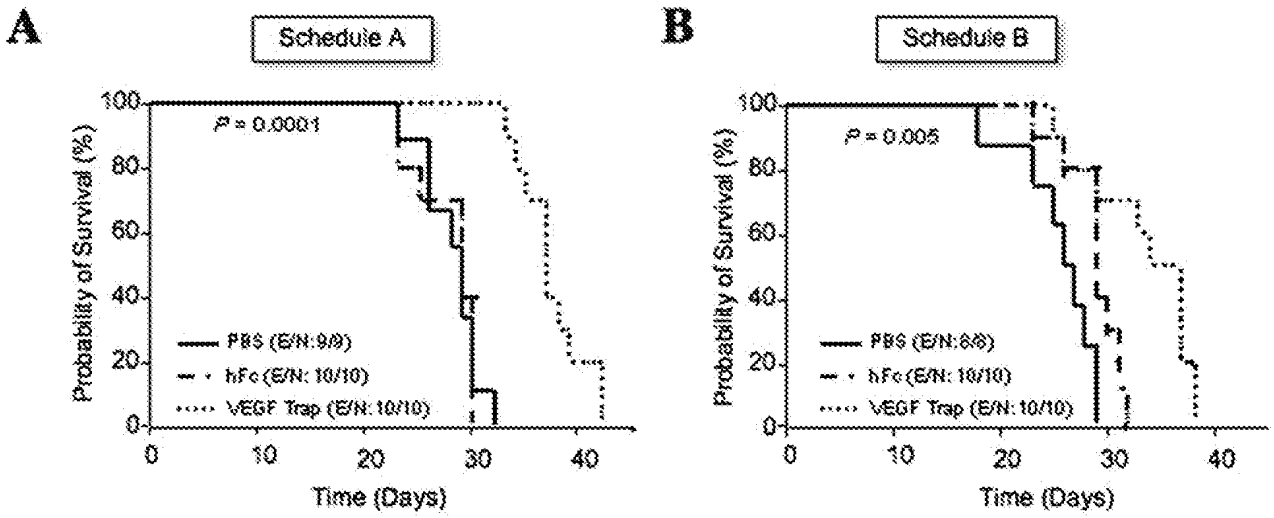


Fig. 2. Effect of the anti-vascular endothelial growth factor (VEGF) agent VEGF Trap on initial phases of disease: survival analysis of glioma-bearing animals treated with VEGF Trap since day 0 (A) or day 4 (B), as pictured in Fig. 1. Kaplan-Meier survival curves begin on the day of U-87 MG intracranial implantation following the subcutaneous injection of VEGF Trap or of vehicle or human Fc (control). The *p*-values (determined by log-rank test) show significant overall survival differences between VEGF Trap-treated and control-treated animals. Abbreviations: E, events; N, number of animals.

Antiglioma Effect of VEGF Trap on Disease Burden

To test the effect of VEGF Trap on tumor burden, and based on our previous study of U-87 MG intracranial growth and angiogenesis, we decided to start treatment on day 10 after cell implantation in one subgroup of mice (Fig. 1, schedule C_S). According to our previous studies, by day 10, increased microvascular density (MVD) was associated with exponential tumor growth and a decrease in the rate of induced angiogenesis within the host and the tumor periphery.[13] Twelve days after implantation, the tumors consisted of spherical masses of cells with a high MVD and large, distorted, SMA-positive vessels. The tumor limits were clearly defined, and the cancer cells did not exhibit the invasive pattern into host tissue seen in preceding days.[13]

In the present study, glioma cells were implanted intracranially, and 10 days later, VEGF Trap was administered subcutaneously at a dose of 25 mg/kg twice weekly for 3 weeks. Control groups were treated with PBS or hFc at doses and volumes similar to those of the test drug. Treatment of the glioma-bearing animals with VEGF Trap resulted in a significant increase in the survival of these animals ($p < 0.005$) (Fig. 3A). In particular, the median overall survival of control-treated (PBS or hFc) animals was 31 days, with all the animals dead by day 33, whereas the mean survival of VEGF Trap-treated animals was 45 days. We observed no significant difference in the effect of VEGF Trap on prolonging survival at different stages of the disease (comparing effects of schedules A and B with schedule C_S) ($p > 0.1$, permutation test), suggesting that VEGF Trap can be similarly effective in both the initial and burden disease stage. These data further suggest that targeting circulating levels of VEGF is equally effective in challenging tumor growth under both initial and established tumoral vasculature phases.

Antiglioma Effect of Prolonged VEGF Trap Treatment

We next explored the effect in vivo of more prolonged VEGF Trap treatment. In this experiment, animals bearing intracranial human gliomas were treated with VEGF Trap (25 mg/kg) twice weekly for 6 weeks starting on day 10 after cell implantation (Fig. 1, schedule C_L). Control animals were treated with vehicle or hFc (25 mg/kg) twice weekly until they showed signs of disease, at which time they were euthanized according to institutional regulations. Animals treated with VEGF Trap for 6 weeks survived longer than did animals treated with hFc (median overall survival, 55 days and 21 days, respectively; Fig. 3B) ($p < 0.0001$). We also analyzed the difference in median survival times between the animals treated with VEGF Trap for 6 weeks and those treated for 3 weeks. Using the permutation test and after adjusting for overall survival on PBS-treated groups, we found the increase in survival obtained with the 6-week VEGF Trap treatment to be significantly greater than the increase in survival obtained with the 3-week treatment ($p < 0.05$). These data suggest that VEGF Trap is more effective in prolonging overall survival when administered in a prolonged treatment schedule.

Histological Examination of VEGF Trap-Treated Tumors

Microscopic analysis of histological sections from formalin-fixed, paraffin-embedded brains revealed that control- and VEGF Trap-treated animals eventually suffered from the lethal growth of their tumors. Because of

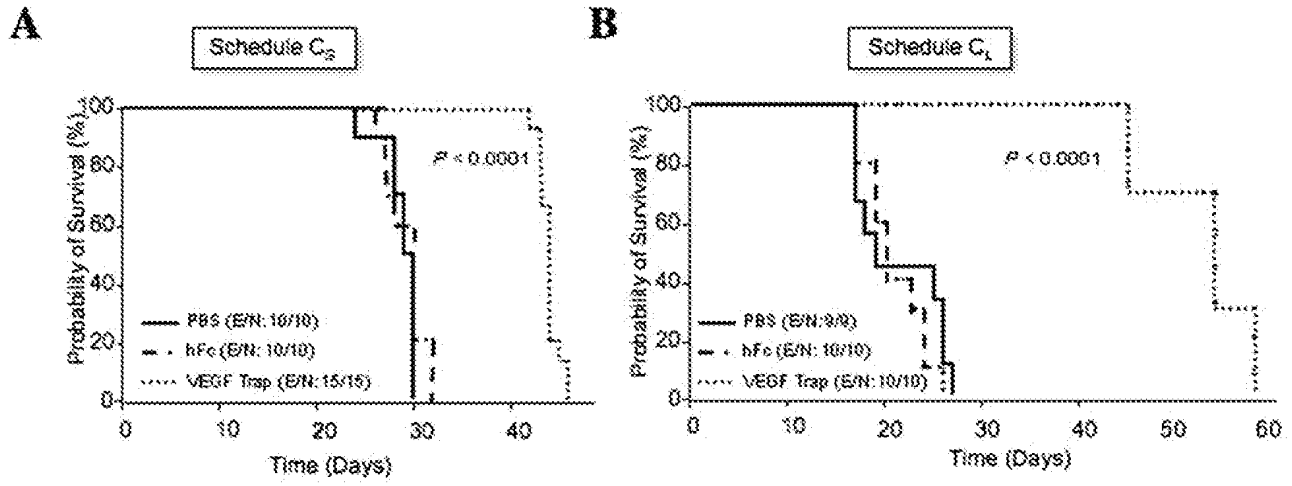


Fig. 3. Effect of the anti-vascular endothelial growth factor (VEGF) agent VEGF Trap on advanced glioma disease: survival analyses of glioma-bearing animals that were treated with VEGF Trap starting on day 10 after cell implantation in either a 3-week (schedule C_S) or 6-week (schedule C_L) regimen, as pictured in Fig. 1. Kaplan-Meier survival curves begin on the day of U-87 MG intracranial implantation following the subcutaneous injection of VEGF Trap or control agent (vehicle or human Fc). The *p*-values (determined by log-rank test) show significant overall survival differences between VEGF Trap-treated and control-treated animals. Abbreviations: E, events; N, number of animals.

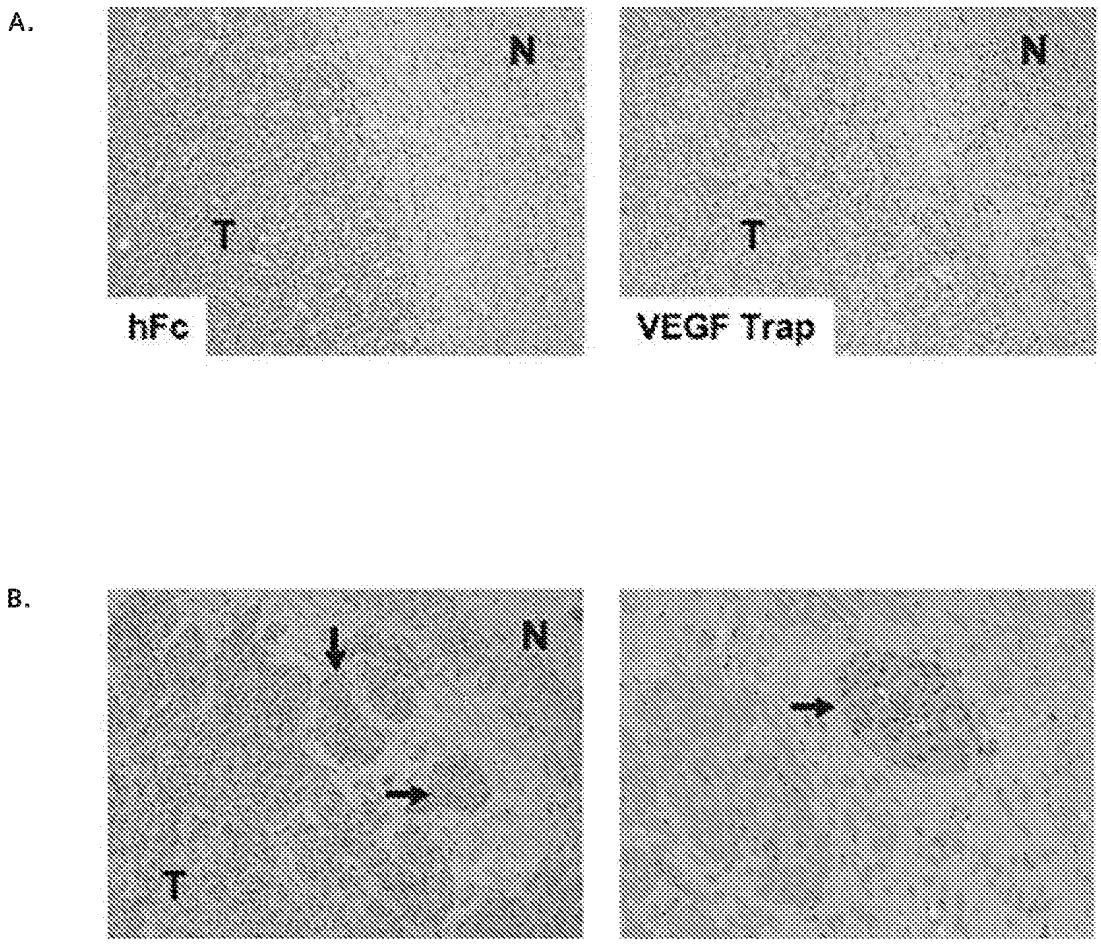


Fig. 4. Histological examination of brain sections from animals treated with the anti-vascular endothelial growth factor (VEGF) agent VEGF Trap. (A) Hematoxylin-eosin staining of mouse brains bearing U-87 MG xenografts treated with human Fc (hFc) or VEGF Trap according to schedule B. No signs of hemorrhagic areas or an enhanced invasive phenotype were observed after VEGF Trap treatment. N, normal tissue; T, tumor tissue. Original magnification, ×100. (B) Histological examination of brain sections from animals treated with VEGF Trap as described for schedule C_L. Sections stained with hematoxylin and eosin show the presence of an invasive phenotype with satellitosis characterized by glioma clustering around vascular vessels and accumulation of invasive glioma cells far from the main tumor mass (arrows). Original magnification: left, ×100; right, ×200.

previous studies describing that treatment with antiangiogenic agents may result in intracranial hemorrhages or enhance tumor invasion,[2,17] we specifically examined the tumors for the presence of these adverse effects. Histological examination of the brains of the cohorts treated for 3 weeks did not reveal either phenomenon. Treated U-87 MG-derived tumors displayed a very well-defined border with the normal host parenchyma (Fig. 4A). However, examination of the brains of animals that received prolonged treatment (6 weeks) of VEGF Trap, which survived longer than those treated on a 3-week schedule, revealed the signs of mass effect and the presence of the so-called "secondary structures" or "satellitosis" consisting of aggregations of glioma cells in the perivascular regions, as well as the presence of glioma cells along the Virchow-Robin spaces (Fig. 4B). These data suggest that U-87 MG-derived xenografts acquired an invasive phenotype in response to anti-VEGF therapy. These results are in agreement with a similar pattern of growth of intracranial G55 xenografts in animals treated with an antibody against mouse VEGFR-2, DC101,[17] or a neutralizing VEGF antibody.[18] These results may be likewise in agreement with those from clinical trials in patients with cancer treated with VEGF inhibitors, in that they survived longer but eventually exhibited resistance to the treatment.[19,20] Of importance, the model described here offers us the possibility of testing combined therapies designed to counteract the emergence of a resistant phenotype to anti-VEGF therapies.

Taken together, our data show that treatment with VEGF Trap significantly prolonged the survival of glioma xenograft-bearing mice. Of great interest, initial/residual disease and disease burden were both similarly affected by the antiangiogenesis treatment. In addition, the prolonged use of VEGF Trap (over 6 weeks) improved outcomes significantly more than did treatment administered in a short schedule (over 3 weeks).

The traits for personalized medicine are emerging

for the treatment of brain tumors, and they will need to take into consideration the highly heterogeneous nature of these tumors.[1,21] However, the fact that all brain tumor subtypes rely on blood vessels for survival and growth indicates the broad applicability of this strategy. Thus, our report provides data that encourage the testing of VEGF Trap in patients with recurrent malignant gliomas, and in this regard, results from a multicenter study consisting of a phase II clinical trial of VEGF Trap in patients with recurrent gliomas will soon be available. Finally, we suggest that VEGF Trap should also be considered for the treatment of patients after extensive surgery, which we would regard as carrying minimal residual disease, in combination with therapies targeting the migratory and invasive properties of gliomas.

Acknowledgments

We greatly thank Drs. John S. Rudge and Risa Shapiro (Regeneron Pharmaceuticals, Inc.) for their useful comments and the ELISA studies, Betty Notzon (Department of Scientific Publications, M. D. Anderson) for editorial assistance, and Verlene Henry and Jennifer Edge for technical assistance (Brain Tumor Center, M. D. Anderson). This work was supported by National Cancer Institute grant CA-16672 (supporting the Research Histopathology and Research Animal Support core facilities at M. D. Anderson) and was partially sponsored by Regeneron Pharmaceuticals, Inc.

J.H. is currently at Novartis Institutes for BioMedical Research, Emeryville, CA, USA.

References

1. Batchelor TT, Sorensen AG, di Tomaso E, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell*. 2007;11:83–95.
2. Pope WB, Lai A, Nghiemphu P, et al. MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy. *Neurology*. 2006;66:1258–1260.
3. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res*. 2007;13:1253–1259.
4. Jain RK, di Tomaso E, Duda DG, et al. Angiogenesis in brain tumours. *Nat Rev Neurosci*. 2007;8:610–622.
5. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A*. 2002;99:11393–11398.
6. Byrne AT, Ross L, Holash J, et al. Vascular endothelial growth factor-trap decreases tumor burden, inhibits ascites, and causes dramatic vascular remodeling in an ovarian cancer model. *Clin Cancer Res*. 2003;9:5721–5728.
7. Kim ES, Serur A, Huang J, et al. Potent VEGF blockade causes regression of coopted vessels in a model of neuroblastoma. *Proc Natl Acad Sci U S A*. 2002;99:11399–11404.
8. Riely GJ, Miller VA. Vascular endothelial growth factor trap in non small cell lung cancer. *Clin Cancer Res*. 2007;13:s4623–s4627.
9. Verheul HM, Hammers H, van Erp K, et al. Vascular endothelial growth factor trap blocks tumor growth, metastasis formation, and vascular leakage in an orthotopic murine renal cell cancer model. *Clin Cancer Res*. 2007;13:4201–4208.
10. Wachsberger PR, Burd R, Cardi C, et al. VEGF trap in combination with radiotherapy improves tumor control in u87 glioblastoma. *Int J Radiat Oncol Biol Phys*. 2007;67:1526–1537.
11. Blouw B, Song H, Tihan T, et al. The hypoxic response of tumors is dependent on their microenvironment. *Cancer Cell*. 2003;4:133–146.
12. Roberts WG, Delaat J, Nagane M, et al. Host microvasculature influence on tumor vascular morphology and endothelial gene expression. *Am J Pathol*. 1998;153:1239–1248.
13. Lee OH, Fueyo J, Xu J, et al. Sustained angiopoietin-2 expression disrupts vessel formation and inhibits glioma growth. *Neoplasia*. 2006;8:419–428.
14. Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. *Nat Rev Cancer*. 2003;3:401–410.
15. Holash J, Maisonpierre PC, Compton D, et al. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science*. 1999;284:1994–1998.
16. Rudge JS, Holash J, Hylton D, Russell M, et al. Inaugural article: VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. *Proc Natl Acad Sci U S A*. 2007;104:18363–18370.
17. Kunkel P, Ulbricht U, Bohlen P, et al. Inhibition of glioma angiogenesis and growth in vivo by systemic treatment with a monoclonal antibody against vascular endothelial growth factor receptor-2. *Cancer Res*. 2001;61:6624–6628.
18. Rubenstein JL, Kim J, Ozawa T, et al. Anti-VEGF antibody treatment of glioblastoma prolongs survival but results in increased vascular cooption. *Neoplasia*. 2000;2:306–314.
19. Kerbel RS, Yu J, Tran J, et al. Possible mechanisms of acquired resistance to anti-angiogenic drugs: implications for the use of combination therapy approaches. *Cancer Metastasis Rev*. 2001;20:79–86.
20. Miller KD, Sweeney CJ, Sledge GW Jr. The snark is a boojum: the continuing problem of drug resistance in the antiangiogenic era. *Ann Oncol*. 2003;14:20–28.
21. Kleihues P, Burger PC, Scheithauer BW. Histological typing of tumours of the central nervous system. 2nd ed. Berlin: Springer; 1993:1–105.

ORIGINAL ARTICLE

Pegaptanib for Neovascular Age-Related Macular Degeneration

Evangelos S. Gragoudas, M.D., Anthony P. Adamis, M.D., Emmett T. Cunningham, Jr., M.D., Ph.D., M.P.H., Matthew Feinsod, M.D., and David R. Guyer, M.D., for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group

ABSTRACT

BACKGROUND

Pegaptanib, an anti–vascular endothelial growth factor therapy, was evaluated in the treatment of neovascular age-related macular degeneration.

METHODS

We conducted two concurrent, prospective, randomized, double-blind, multicenter, dose-ranging, controlled clinical trials using broad entry criteria. Intravitreous injection into one eye per patient of pegaptanib (at a dose of 0.3 mg, 1.0 mg, or 3.0 mg) or sham injections were administered every 6 weeks over a period of 48 weeks. The primary end point was the proportion of patients who had lost fewer than 15 letters of visual acuity at 54 weeks.

RESULTS

In the combined analysis of the primary end point (for a total of 1186 patients), efficacy was demonstrated, without a dose–response relationship, for all three doses of pegaptanib ($P<0.001$ for the comparison of 0.3 mg with sham injection; $P<0.001$ for the comparison of 1.0 mg with sham injection; and $P=0.03$ for the comparison of 3.0 mg with sham injection). In the group given pegaptanib at 0.3 mg, 70 percent of patients lost fewer than 15 letters of visual acuity, as compared with 55 percent among the controls ($P<0.001$). The risk of severe loss of visual acuity (loss of 30 letters or more) was reduced from 22 percent in the sham-injection group to 10 percent in the group receiving 0.3 mg of pegaptanib ($P<0.001$). More patients receiving pegaptanib (0.3 mg), as compared with sham injection, maintained their visual acuity or gained acuity (33 percent vs. 23 percent; $P=0.003$). As early as six weeks after beginning therapy with the study drug, and at all subsequent points, the mean visual acuity among patients receiving 0.3 mg of pegaptanib was better than in those receiving sham injections ($P<0.002$). Among the adverse events that occurred, endophthalmitis (in 1.3 percent of patients), traumatic injury to the lens (in 0.7 percent), and retinal detachment (in 0.6 percent) were the most serious and required vigilance. These events were associated with a severe loss of visual acuity in 0.1 percent of patients.

CONCLUSIONS

Pegaptanib appears to be an effective therapy for neovascular age-related macular degeneration. Its long-term safety is not known.

From the Massachusetts Eye and Ear Infirmary, Boston (E.S.G.); and Eyetech Pharmaceuticals, New York (A.P.A., E.T.C., M.F., D.R.G.). Address reprint requests to Dr. Gragoudas at the Retina Service, Massachusetts Eye and Ear Infirmary and Harvard Medical School, 243 Charles St., Boston, MA 02114, or at evangelos_gragoudas@meei.harvard.edu.

N Engl J Med 2004;351:2805-16.

THE USE OF A SPECIFIC ANTAGONIST OF an angiogenic factor as a strategy to treat disease was proposed in the *Journal* more than 30 years ago.[1] Since that time, extensive evidence has suggested a causal role of vascular endothelial growth factor (VEGF) in several diseases of the human eye in which neovascularization and increased vascular permeability occur.[1-12] In humans, ocular VEGF levels have been shown to rise synchronously with and in proportion to the growth and leakage of new vessels.[2-4] Animal models of corneal,[5] iridic,[6] retinal,[7] and choroidal[8] neovascularization have shown that neovascularization is dependent on the presence of VEGF. In a complementary fashion, the introduction of VEGF into normal animal eyes resulted in a recapitulation of the pathologic neovascularization that occurs in these tissues during disease.[9-12] Taken together, these data provided a strong rationale for the targeting of VEGF in human disorders that manifest as ocular neovascularization and increased vascular permeability.

Age-related macular degeneration is the leading cause of irreversible, severe loss of vision in people 55 years of age and older in the developed world, and it remains an area of unmet medical need.[13] The neovascular form of the disease represents approximately 10 percent of the overall disease prevalence, but it is responsible for 90 percent of the severe vision loss.[14] It is expected to develop in almost 1 million people over the age of 55 years in the United States within the next five years, making it a major public health issue in an increasing population of older persons.[15]

Neovascular age-related macular degeneration is characterized by choroidal neovascularization that invades the subretinal space, often leading to exudation and hemorrhage. If the condition is left untreated, damage to photoreceptors and loss of central vision usually result, and after several months to years, the vessels are largely replaced by a fibrovascular scar.[16-18] Patients in whom a central scotoma develops have difficulty performing critical tasks that are typically associated with central vision, such as reading, driving, walking, and recognizing faces, and the difficulty has a major effect on their quality of life.[19]

With greater understanding of the pathogenesis of neovascular age-related macular degeneration, drug therapies targeted at the causal molecular mechanisms have been advanced. Pegaptanib (Macugen), a 28-base ribonucleic acid aptamer (from the Latin *aptus,* to fit; and the Greek *meros,* part or region) covalently linked to two branched 20-kD polyethylene glycol moieties, was developed to bind and block the activity of extracellular VEGF, specifically the 165-amino-acid isoform ($VEGF_{165}$). Aptamers characteristically bind with high specificity and affinity to target molecules, including proteins. The binding relies on the specific three-dimensional conformation of the properly folded aptamer. To prolong activity at the site of action, the sugar backbone of pegaptanib was modified to prevent degradation by endogenous endonucleases and exonucleases, and the polyethylene glycol moieties were added to increase the half-life of the drug in the vitreous.[20]

We hypothesized that the targeting of $VEGF_{165}$ would affect the underlying conditions common to all forms of choroidal neovascularization, including the three angiographic subtypes of neovascular age-related macular degeneration. We conducted two concurrent clinical trials to test the short-term safety and effectiveness of pegaptanib in patients with a broad spectrum of visual acuities, lesion sizes, and angiographic subtypes of lesions at baseline.

METHODS

STUDY DESIGN

We conducted two concurrent, prospective, randomized, double-blind, multicenter, dose-ranging, controlled clinical trials at 117 sites in the United States, Canada, Europe, Israel, Australia, and South America in our study. Patients were eligible for inclusion if they were 50 years of age or older and had subfoveal sites of choroidal neovascularization secondary to age-related macular degeneration and a range of best corrected visual acuity of 20/40 to 20/320 in the study eye and of 20/800 or better in the other eye.

The angiographic subtype of a patient's lesion was defined in relation to the visualization of choroidal new vessels (classic) in the fluorescein angiogram. The total area of a predominantly classic lesion includes more than 50 percent classic choroidal neovascularization, the total area of a minimally classic lesion includes less than 50 percent classic choroidal neovascularization, and the total area of an occult lesion includes no classic choroidal neovascularization. The total size of a lesion, choroidal neovascularization, or leakage was measured on a frame on the fluorescein angiogram with the optic-disk area as the unit of measure; it is equal to 2.54 mm^2. The size of a lesion, choroidal

neovascularization, or leakage is expressed as multiples of this standard optic-disk area.

Patients with all angiographic subtypes of lesions were enrolled, and lesions with a total size up to and including 12 optic-disk areas (including blood, scar or atrophy, and neovascularization) were permitted. Details of the method are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

TREATMENT AND OUTCOMES

Patients were randomly assigned to receive either sham injection or intravitreous injection of pegaptanib (Macugen, Eyetech Pharmaceuticals) into one eye every 6 weeks over a period of 48 weeks, for a total of nine treatments. To maintain masking of the patients, the patients receiving sham injections and those receiving the study medication were treated identically, with the exception of scleral penetration. All patients (including those receiving sham injection) underwent an ocular antisepsis procedure and received injected subconjunctival anesthetic. The patients receiving sham injections had an identical syringe — but without a needle — pressed against the eye wall to mimic the active doses that were injected through the pars plana into the vitreous cavity. The injection technique precluded the patient from seeing the syringe. To maintain masking of the investigators, the study ophthalmologist responsible for patient care and for the assessments did not administer the injection. In all cases, a separate, certified visual-acuity examiner masked to the treatment assignment and to previous measurements of visual acuity assessed distance visual acuity.

Owing to ethical considerations, the use of photodynamic therapy with verteporfin was permitted only in the treatment of patients with predominantly classic lesions, as defined in the product label approved by the Food and Drug Administration, and at the discretion of the ophthalmologist, who was masked as to the treatment assignment. The prespecified primary end point for efficacy was the proportion of patients who lost fewer than 15 letters of visual acuity (defined as three lines on the study eye chart) between baseline and week 54.

The trials were designed by the steering committee of the VEGF [Vascular Endothelial Growth Factor] Inhibition Study in Ocular Neovascularization Clinical Trial Group. The data were held and analyzed by the data management and statistics group. The manuscript was prepared by the writing committee. Dr. Gragoudas chaired the writing committee, served as the outside academic investigator vouching for the veracity and completeness of the data analyses, had access to the full data set, and was responsible for the decision to submit the manuscript for publication.

RESULTS

One trial included 586 patients at 58 sites in the United States and Canada and was conducted from August 2001 through July 2002; the other trial included 622 patients at 59 other sites worldwide and was conducted from October 2001 through August 2002. Of the 1208 patients randomly assigned to treatment in the two studies (297 patients assigned to receive 0.3 mg of pegaptanib; 305 patients, 1.0 mg of pegaptanib; 302 patients, 3.0 mg of pegaptanib; and 304 patients, sham injections), 1190 received at least one study treatment (295 patients received 0.3 mg of pegaptanib; 301 patients, 1.0 mg of pegaptanib; 296 patients, 3.0 mg of pegaptanib; and 298 patients, sham injections). The demographic and ocular characteristics of the patients at baseline were similar among the treatment groups (Table 1).

Four patients were not included in the efficacy analyses, because a sufficiently standardized assessment of visual acuity was not completed at baseline. Therefore, a total of 1186 patients received at least one study treatment, had visual acuity assessments at baseline, and were included in efficacy analyses (294 patients who received 0.3 mg of pegaptanib; 300 patients, 1.0 mg of pegaptanib; 296 patients, 3.0 mg of pegaptanib; and 296 patients, sham injections). A total of 7545 intravitreous injections of pegaptanib and 2557 sham injections were administered. Approximately 90 percent of the patients in each treatment group completed the study. In all the treatment groups, an average of 8.5 injections were administered per patient out of a possible total of 9 injections.

The general health status of the patients entering the trial, calculated for all patients receiving pegaptanib as compared with those receiving sham injection, was as follows: hypertension (55 percent in the pegaptanib groups vs. 48 percent in the sham-injection group), hypercholesterolemia (21 percent vs. 18 percent), diabetes mellitus (10 percent vs. 7 percent), cardiac disorders (35 percent vs. 34 percent), cerebrovascular disease (3 percent vs. 1 percent), peripheral arterial disease (3 percent vs.

Table 1. **Demographic and Ocular Characteristics of Patients at Baseline.***

Characteristic	0.3 mg Pegaptanib (N=295)	1.0 mg Pegaptanib (N=301)	3.0 mg Pegaptanib (N=296)	Sham Injection (N=298)
Sex — no. (%)				
Male	133 (45)	136 (45)	105 (35)	120 (40)
Female	162 (55)	165 (55)	191 (65)	178 (60)
Race — no. (%)†				
White	283 (96)	291 (97)	286 (97)	284 (95)
Other	12 (4)	10 (3)	10 (3)	14 (5)
Age — no. (%)				
50–64 yr	19 (6)	21 (7)	18 (6)	21 (7)
65–74 yr	86 (29)	105 (35)	90 (30)	94 (32)
75–84 yr	155 (53)	147 (49)	153 (52)	160 (54)
≥85 yr	35 (12)	28 (9)	35 (12)	23 (8)
Angiographic subtype of lesion — no. (%)‡				
Predominantly classic	72 (24)	78 (26)	80 (27)	76 (26)
Minimally classic	111 (38)	108 (35)	105 (35)	102 (34)
Occult with no classic	112 (38)	115 (38)	111 (38)	120 (40)
Size of lesion§	3.7±2.4	4.0±2.4	3.7±2.5	4.2±2.8
History of ocular surgery or laser treatment — no. (%)	123 (42)	117 (39)	124 (42)	124 (42)
Visual acuity				
Study eye				
Mean	52.8±12.6	50.7±12.8	51.1±12.9	52.7±13.0
Median (range)	55 (11–75)	52 (19–77)	53 (14–76)	53 (11–77)
Other eye				
Mean	56.2±27.2	54.8±27.6	56±26.4	55.9±27.0
Median (range)	68 (3–85)	67 (3–85)	65 (4–85)	67 (2–85)

* Plus–minus values are means ±SD.
† Race was determined by the treating investigators.
‡ In relation to the visualization of choroidal new vessels (classic) in the fluorescein angiogram, a predominantly classic lesion includes 50 percent or more classic choroidal neovascularization, a minimally classic lesion includes less than 50 percent classic choroidal neovascularization, and an occult lesion includes no classic choroidal neovascularization.
§ The size of lesions was measured as the number of optic-disk areas (including blood scar or atrophy and neovascularization), each of which is 2.54 mm^2.

3 percent), and electrocardiographic abnormalities (53 percent vs. 48 percent).

In the combined analysis, all three doses of pegaptanib differed significantly from the sham injection in terms of the prespecified primary efficacy end point (Table 2). A loss of fewer than 15 letters of visual acuity was observed at week 54 in 206 (70 percent) of 294 patients assigned to receive 0.3 mg of pegaptanib (P<0.001), 213 (71 percent) of 300 patients assigned to 1.0 mg of pegaptanib (P<0.001), and 193 (65 percent) of 296 patients assigned to 3.0 mg of pegaptanib (P=0.03), as compared with 164 (55 percent) of 296 patients assigned to receive sham injection. Similar results were obtained when the analyses were restricted to the subgroup of patients who were evaluated both at baseline and at week 54 (accounting for 92 percent of those receiving 0.3 mg of pegaptanib, 92 percent of those receiving 1.0 mg of the drug, 89 percent of those receiving 3.0 mg of the drug, and 93 percent of those receiving sham injections); the similar findings indicate that missing data probably did not influence the results. In this population at week 54, a loss of fewer than 15 letters was observed in 192 (71 percent) of

Table 2. **Rate of Visual-Acuity Loss, Measured as the Loss of Fewer Than 15 Letters, in 1186 Patients.***

Time	0.3 mg Pegaptanib (N=294)		1.0 mg Pegaptanib (N=300)		3.0 mg Pegaptanib (N=296)		Sham Injection (N=296)
	No. (%)	P Value vs. Sham Injection	No. (%)	P Value vs. Sham Injection	No. (%)	P Value vs. Sham Injection	No. (%)
Week 12	256 (87)	0.01	259 (86)	0.04	251 (85)	0.13	237 (80)
Week 24	242 (82)	<0.001	239 (80)	<0.001	224 (76)	0.003	190 (64)
Week 36	220 (75)	<0.001	229 (76)	<0.001	222 (75)	<0.001	175 (59)
Week 54	206 (70)	<0.001	213 (71)	<0.001	193 (65)	0.03	164 (55)

* The differences between the doses of pegaptanib were not significant.

271 patients assigned to receive 0.3 mg of pegaptanib (P<0.001), 198 (72 percent) of 275 patients assigned to 1.0 mg of the study drug (P<0.001), and 166 (63 percent) of 264 patients assigned to 3.0 mg of pegaptanib (P=0.14), as compared with 154 (56 percent) of 275 patients assigned to sham injection. There was no evidence in any of the analyses that pegaptanib at 1.0 mg or 3.0 mg was more effective than at 0.3 mg. The results of the two trials were similar, with both reaching statistical significance for the primary efficacy end point (0.3 mg of pegaptanib, P=0.03 and P=0.01).

The outcomes for the secondary end points were consistent with those for the primary end point. A greater proportion of the patients treated with pegaptanib maintained or gained visual acuity (that is, they had no change in the number of letters or a gain of one or more letters). For the combined analysis, 33 percent of patients receiving 0.3 mg of pegaptanib (P=0.003), 37 percent of those receiving 1.0 mg (P<0.001), and 31 percent of those receiving 3.0 mg (P=0.02) maintained vision or gained vision as compared with 23 percent of those receiving sham injection. At week 54, larger proportions of patients receiving pegaptanib, as compared with those receiving sham injection, also gained 5, 10, or 15 letters of visual acuity (approximately equivalent to one, two, and three lines on the study eye chart, respectively) (Table 3).

Patients in the sham-injection group were twice as likely to have a severe loss of vision (i.e., a loss of 30 letters or more or six lines on the study eye chart) as patients receiving pegaptanib at 0.3 mg (22 percent vs. 10 percent, P<0.001) or 1.0 mg (22 percent vs. 8 percent, P<0.001). Among patients receiving a dose of 3.0 mg, 14 percent had severe vision loss (P=0.01 for the comparison with the sham-injection group) (Table 3).

A smaller percentage of patients receiving pegaptanib had a Snellen equivalent visual acuity of 20/200 or worse, or legal blindness, in the study eye at week 54 than of those in the sham-injection group (pegaptanib at 0.3 mg, 38 percent; 1.0 mg, 43 percent; 3.0 mg, 44 percent; sham injection, 56 percent; P<0.001 for the comparison between all treatment groups and the sham-injection group) (Table 3).

The effectiveness of pegaptanib was evident as early as the first study visit after the treatment was started (week 6), and it increased over time up to week 54, as measured by the mean loss of visual acuity from baseline to each study visit as compared with that in the sham-injection group (P<0.002 at every point for a dose of pegaptanib at 0.3 mg or 1.0 mg, and P<0.05 at every point for a dose of 3.0 mg) (Fig. 1A).

There was no evidence that any angiographic subtype of the lesion, the size of the lesion, or the level of visual acuity at baseline precluded a treatment benefit. For those receiving pegaptanib at 0.3 mg, a treatment benefit was observed among all patients with all angiographic subtypes of lesions (P<0.03 for each subtype) (Fig. 1B), baseline levels of visual acuity (<54 or ≥54 letters, P<0.01 for each group) (Fig. 1C), and lesion sizes at baseline (<4 or ≥4 optic-disk areas, P<0.02 for each group) (Fig. 1D). Numerically superior outcomes were observed among patients with different subtypes of lesions treated with pegaptanib at 1.0 mg and 3.0 mg as well (Fig. 1B). The results of multiple logistic-regression analyses revealed that no factor other than assignment to treatment with pegaptanib was

Table 3. **Maintenance, Gain, and Severe Loss of Visual Acuity with Pegaptanib and Sham Injection.***

End Points	0.3 mg Pegaptanib (N=294)	1.0 mg Pegaptanib (N=300)	3.0 mg Pegaptanib (N=296)	Sham Injection (N=296)
Maintenance or gain ≥0 letters — no. (%)	98 (33)	110 (37)	93 (31)	67 (23)
P value vs. sham injection	0.003	<0.001	0.02	
Gain ≥5 letters — no. (%)	64 (22)	69 (23)	49 (17)	36 (12)
P value vs. sham injection	0.004	0.002	0.12	
Gain ≥10 letters — no. (%)	33 (11)	43 (14)	31 (10)	17 (6)
P value vs. sham injection	0.02	0.001	0.03	
Gain ≥15 letters — no. (%)	18 (6)	20 (7)	13 (4)	6 (2)
P value vs. sham injection	0.04	0.02	0.16	
Loss ≥30 letters — no. (%)	28 (10)	24 (8)	40 (14)	65 (22)
P value vs. sham injection	<0.001	<0.001	0.01	
Visual acuity in study eye ≤20/200 (legal blindness) — no. (%)	111 (38)	128 (43)	129 (44)	165 (56)
P value vs. sham injection	<0.001	<0.001	0.001	

* Where data were missing, the last-observation-carried-forward method was used. P values were calculated with the use of the Cochran–Mantel–Haenszel test. Loss of 30 or more letters was defined as severe loss of visual acuity.

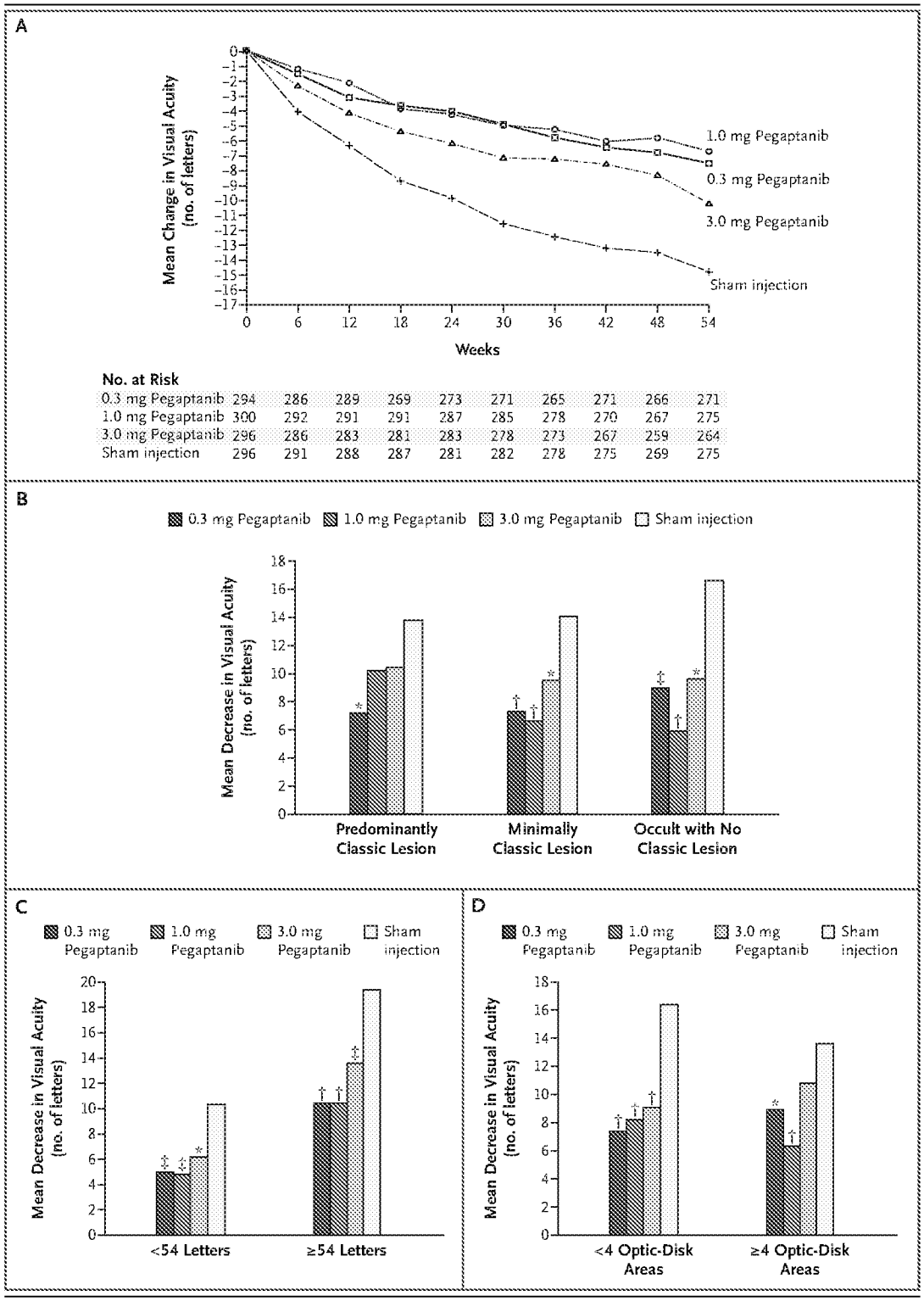
significantly associated with this response (0.3-mg dose, P<0.001).

The majority (78 percent) of the study patients never received photodynamic therapy while in the study (at or after the baseline evaluation), and 75 percent of the patients never received photodynamic therapy at any time (i.e., they had no history of photodynamic therapy, nor did they receive the treatment during the study) in the study eye. The rate of use of this therapy before enrollment and at baseline was similar among the treatment groups; therapy before enrollment was used for stratification at randomization. A history of photodynamic therapy was reported at baseline by 24 patients receiving pegaptanib at 0.3 mg (8 percent), 29 patients receiving 1.0 mg (10 percent), 27 patients receiving 3.0 mg (9 percent), and 18 patients receiving sham injections (6 percent).

The study investigators administered photodynamic therapy at baseline to 36 patients receiving 0.3 mg of pegaptanib (12 percent), 31 patients receiving 1.0 mg (10 percent), 38 patients receiving 3.0 mg (13 percent), and 40 patients receiving sham injections (13 percent). A slightly higher proportion of patients receiving sham injections than those receiving pegaptanib received photodynamic therapy after baseline, suggesting a possible bias against pegaptanib. After baseline, photodynamic therapy was administered to 49 patients receiving 0.3 mg of pegaptanib (17 percent), 55 patients receiving 1.0 mg (18 percent), 57 patients receiving 3.0 mg (19 percent), and 62 patients receiving sham injections (21 percent). Therefore, the treatment benefit of pegaptanib was present despite the higher rate

Figure 1 (facing page). **Mean Change in Scores for Visual Acuity.**

Panel A shows the mean changes in visual acuity from baseline to week 54 (P<0.002 at every point for the comparison of 0.3 mg or 1.0 mg of pegaptanib with sham injection at week 54, and P<0.05 at every point for the comparison of 3.0 mg of pegaptanib with sham injection at all other points after baseline). Panels B, C, and D show the mean changes in visual acuity according to the angiographic subtype, visual acuity, and lesion size at baseline, respectively. In relation to the visualization of choroidal new vessels (classic) in the fluorescein angiogram, a predominantly classic lesion includes 50 percent or more classic choroidal neovascularization, a minimally classic lesion includes less than 50 percent classic choroidal neovascularization, and an occult lesion includes no classic choroidal neovascularization. For lesion size, the unit of measurement was one optic-disk area, equal to 2.54 mm². For this analysis, lesions were categorized as less than four optic-disk areas or four or more optic-disk areas in size. In Panels B, C, and D, the asterisk denotes P<0.05 for the comparison of pegaptanib with sham injection, the single dagger P<0.001 for the comparison of pegaptanib with sham injection, and the double dagger P<0.01 for the comparison of pegaptanib with sham injection. Of a total of 1186 patients, 294 received 0.3 mg of pegaptanib, 300 received 1.0 mg of pegaptanib, 296 received 3.0 mg of pegaptanib, and 296 received sham injection.



of use of photodynamic therapy among patients receiving sham injections.

On the two angiographic examinations, there was a slowing in the growth of the total area of a lesion, the size of choroidal neovascularization, and the severity of leakage in the groups receiving pegaptanib as compared with the sham-injection group (Table 4). A difference was evident at weeks 30 and 54.

The rate of discontinuation of therapy due to adverse events was 1 percent in the pegaptanib groups and 1 percent in the sham-injection group. The reasons for discontinuation were diverse and were not clustered in relation to a particular system or organ. No systemic adverse events were definitively attributed by the independent data management and safety monitoring committee to the study drug, nor were any observed for any organ system in all three treatment groups. In a comparison of rates of adverse events (for all doses of pegaptanib as compared with sham injection), no significant difference was observed in the rates of vascular hypertensive disorders (10 percent in all groups); hemorrhagic adverse events (2 percent and 3 percent, respectively); thromboembolic events (6 percent in all groups), and gastrointestinal perforations (0 in all groups). The baseline laboratory values were similar in all groups, and median changes in all laboratory values from baseline were small and not clinically meaningful. The death rate was 2 percent in all groups, which is similar to that seen in other studies of age-related macular degeneration in this population.[21] No antibodies against pegaptanib were detected. There were also no reports of local or systemic hypersensitivity attributable to pegaptanib.

Most adverse events reported in the study eyes were transient, with a severity that was mild to moderate, and were attributed by the investigators to the injection procedure, rather than to the study drug. Common ocular adverse events that occurred more frequently in the study eyes of patients treated with pegaptanib than in those receiving sham injection were eye pain (34 percent vs. 28 percent), vitreous floaters (33 percent vs. 8 percent, P<0.001), punctate keratitis (32 percent vs. 27 percent), cataracts (20 percent vs. 18 percent), vitreous opacities (18 percent vs. 10 percent, P<0.001), anterior-chamber inflammation (14 percent vs. 6 percent, P=0.001), visual disturbance (13 percent vs. 11 percent), eye discharge (9 percent vs. 8 percent), and corneal edema (10 percent vs. 7 percent).

These events were more common in the study eyes than in the other eyes among patients in the sham-injection group, suggesting that the events were in part a result of the preparation procedure for injection, as opposed to the study drug. There was no evidence of a sustained elevation in intraocular pressure or of an acceleration of the formation of a cataract among patients in the treatment groups as compared with those in the sham-injection group. A masked review by the reading center at the University of Wisconsin of all angiograms obtained at baseline and at weeks 30 and 54 revealed no evidence of adverse effects on the retinal or the choroidal vascular beds.

Injection-related adverse events are summarized in Table 5. Endophthalmitis, a potentially serious intraocular infection that may result in the loss of visual acuity, is thought possibly to result from the intravitreous route of administration. Of the 12 patients (1.3 percent of 890 receiving pegaptanib) in whom endophthalmitis developed over the period of 54 weeks, 1 patient (0.1 percent of all treated patients, and 8 percent of those with endophthalmitis) had a loss of 30 letters or more of visual acuity (i.e., visual acuity decreased from 20/63 at baseline to 20/800 at the last patient visit) in association with the infection. Two thirds of the patients with en-

Table 4. Changes in Size of Lesion, Extent of Choroidal Neovascularization (CNV), and Leakage over Time in 1186 Patients.

Variable*	0.3 mg Pegaptanib (N=294)	1.0 mg Pegaptanib (N=300)	3.0 mg Pegaptanib (N=296)	Sham Injection (N=296)
Total size of lesion				
Baseline	3.7	4.0	3.7	4.2
Wk 30	4.9	5.0	5.2	5.7
Wk 54	5.5†	5.8†	6.2	6.7
Total size of CNV				
Baseline	3.1	3.5	3.2	3.7
Wk 30	4.0	4.2	4.2	4.9
Wk 54	4.7	4.7†	5.0	5.8
Total size of leakage				
Baseline	3.3	3.4	3.4	3.6
Wk 30	4.0†	3.6†	4.2	4.9
Wk 54	4.3	3.9†	4.6	5.2

* The total size of a lesion, choroidal neovascularization, or leakage was measured as the number of optic-disk areas, each of which is equal to 2.54 mm^2.
† P<0.01 for the comparison of the change from baseline with that in the sham-injection group.

dophthalmitis had a positive culture. Coagulase-negative *Staphylococcus epidermiditis* was the most common isolate. All patients with clinical endophthalmitis were treated with intravitreous antibiotics. In 8 of the 12 patients with endophthalmitis (67 percent), the infection was associated with protocol violations, the most common being failure to use an eyelid speculum, an instrument that prevents the bacteria on the eyelashes from contaminating the injection site.

DISCUSSION

Pegaptanib produced a statistically significant and clinically meaningful benefit in the treatment of neovascular age-related macular degeneration. Overall, a reduced risk of visual-acuity loss was observed with all doses as early as six weeks after treatment was begun, with evidence of an increasing benefit over time up to week 54 (Fig. 1A). This observation was supported by a variety of findings. Pegaptanib reduced the chance not only of the loss of 15 letters or more of visual acuity (considered a moderate loss), but also of a loss of 30 letters or more (six lines on the study eye chart, which is considered a severe loss). In addition, treatment with pegaptanib reduced the risk of progression to legal blindness in the study eye, promoted stability of vision, and in a small percentage of the patients, resulted in more visual improvement at week 54 than among those receiving sham injections.

The visual results are further supported by angiographic measurements obtained by personnel masked to the treatment assignments, which suggested a reduction in the growth of the total size of the lesion or of choroidal neovascularization and in the severity of leakage (Table 4). These data provide indirect biologic evidence of the mechanism of action of pegaptanib. Although fluorescein angiography is a time-honored method of assessing neovascular age-related macular degeneration, the quantitative measurements of the size of a lesion and of choroidal neovascularization may have been confounded by changes in permeability that accompanied pegaptanib therapy. Any conclusions about the extent of choroidal neovascularization and lesion size must be made, therefore, with this caveat in mind. The inhibition of permeability by pegaptanib may have played an important role in the visual outcomes observed. A reduction in vascular permeability probably accounted for the improved outcome at six weeks, because the data indicate there was little likelihood of a meaningful change in choroidal neovascularization or lesion size at that point.

Because all forms of choroidal neovascularization have been associated with elevated levels of VEGF, it was hypothesized that a broad spectrum of patients might benefit from anti-VEGF therapy with pegaptanib. Indeed, there was no evidence that any one baseline characteristic, including angiographic subtype, lesion size, or initial level of visual acuity, precluded a treatment benefit. The beneficial responses observed with pegaptanib probably imply that a common underlying disease process was treated. These data support the hypothesis that pegaptanib is effective in a broad population of patients with neovascular age-related macular degeneration. Since approximately 90 percent of the patients enrolled completed the two trials, the intravitreous-injection regimen also appeared to be accepted by both patients and physicians.

The per-injection rates of endophthalmitis (0.16 percent), retinal detachment (0.08 percent), and traumatic lens injury (0.07 percent) in the current trial were similar to rates identified in a comprehensive review of more than 15,000 intravitreous injections.[22] Therefore, the risks associated with intraocular injection of pegaptanib are probably no different from those associated with intraocular injection of other drugs. Because this treatment requires multiple injections, the risk of endophthalmitis was 1.3 percent per patient during the first year of the trials. For comparison, the range of the reported risk of endophthalmitis associated with cat-

Table 3. **Injection-Related Adverse Events in 890 Patients Treated with Pegaptanib in the First Year of the Trial.***

Adverse Event	Events		Severe Loss of Visual Acuity†
	no. of patients (%)	*per injection (%)*	*no. of patients (%)*
Endophthalmitis	12 (1.3)‡	0.16	1 (0.1)
Traumatic injury to the lens	5 (0.6)	0.07	1 (0.1)
Retinal detachment	6 (0.7)	0.08	0§

* A total of 7545 intravitreous injections of pegaptanib were administered.
† Severe loss of visual acuity is defined as a loss of 30 letters or more.
‡ Three quarters of the patients with endophthalmitis remained in the trial; among the patients with endophthalmitis, the condition was associated with protocol violations in two thirds.
§ Measurements of visual acuity after the event were not available for one patient.

aract surgery is 0.06 percent to 0.4 percent. Our data show that, despite this risk, the majority of patients fare better with eight to nine injections over the course of a year than with no treatment. However, in order to maximize the benefit of treatment, it is critical that all treating ophthalmologists carefully adhere to an appropriate aseptic technique for each injection, educate patients regarding worrisome symptoms, and closely monitor patients after each injection. Careful attention to the technique of the procedure can probably minimize the risk of endophthalmitis after intravitreous injection.[23]

For ethical reasons, sham injection was used as a control in these studies. Preclinical experiments have shown that it is unlikely that control intravitreous injections would have resulted in a visual improvement. Endogenous VEGF-induced retinal vascular permeability in a rat model was not inhibited when phosphate-buffered saline or an inactive control (e.g., polyethylene glycol) was given by intravitreous injection. Only intravitreous injections of pegaptanib reduced vascular permeability.[24] Similarly, studies in primates have shown that intravitreous injections of a VEGF inhibitor effectively suppressed neovascularization in the iris and the choroid, whereas intravitreous injections of inactive control substances such as phosphate-buffered saline or nonimmune antibody did not appear to alter the natural course of the disease.[6,8]

In summary, treatment with pegaptanib provided a statistically significant and clinically meaningful benefit in a broad spectrum of patients with neovascular age-related macular degeneration, regardless of the size or angiographic subtype of the lesion or the baseline visual acuity. The rate of injection-related adverse events represents a potentially modifiable risk but necessitates vigilance. Because age-related macular degeneration tends to progress over years, long-term data will be required for a full characterization of the safety and efficacy of pegaptanib therapy. Our results provide validation of aptamer-based therapy in the treatment of human disease and support ongoing investigations into the use of VEGF antagonists in patients with diabetic retinopathy and retinal-vein occlusion, which are other disorders associated with elevated levels of intraocular VEGF.

Supported by Eyetech Pharmaceuticals and Pfizer.

Dr. Gragoudas reports having served as a paid consultant for Eyetech Pharmaceuticals and Neovista and receiving royalty income from Coherent, the manufacturer of a laser used in photodynamic therapy; Drs. Adamis, Cunningham, Guyer, and Feinsod are employees of and shareholders in Eyetech Pharmaceuticals.

We are indebted to the patients who volunteered for this study.

APPENDIX

The following investigators, data managers, and research coordinators participated in the VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group study: Writing Committee — E.S. Gragoudas (chair and corresponding author), A.P. Adamis, E.T. Cunningham, Jr., D.R. Guyer, M. Feinsod; Steering Committee — M. Blumenkranz, Stanford University; M. Buyse, International Drug Development Institute; M. Goldberg, Johns Hopkins University; E.S. Gragoudas, J. Miller, Massachusetts Eye and Ear Infirmary; S.D. Schwartz, University of California at Los Angeles; L. Singerman, Retina Associates of Cleveland; L. Yannuzzi, Columbia University; A.P. Adamis, D.R. Guyer, D. O'Shaughnessy, Eyetech Pharmaceuticals; Independent Data Management and Safety Monitoring Committee — A. Bird, Moorfields Eye Hospital (chair); D. D'Amico, Massachusetts Eye and Ear Infirmary (chair emeritus); J. Herson; R. Klein, University of Wisconsin; H. Lincoff, New York–Presbyterian Weill Cornell Center; A. Patz, Wilmer Eye Institute; Data Management and Statistics Group — M. Buyse, S. de Gronckel, G. Fesneau, E. Quinaux, D. Tremolet, K. Wang, International Drug Development Institute, Brussels and Boston; A. Brailey, J. Finman, N. Ting, Pfizer, Groton, Conn.; Eligibility and Classification Quality Assurance Team — N.M. Bressler, S.B. Bressler, R. Denblow, O.D. Schein, S. Seabrook, S. Solomon, A.P. Schachat, D. Philips, Wilmer Ophthalmological Institute, Johns Hopkins University; Independent Fundus Photograph and Angiogram Reading Center — M. Altaweel, M.D. Davis, B.A. Blodi, R.P. Danis, M.S. Ip, C. Hiner, J. Elledge, M. Webster, C. Hannan, J. Ficken, S. Alexander, M. Neider, H. Wabers, P. Vargo, E. Lambert, L. Kastorff, A. Carr, A. Shkiele, J. Baliker, University of Wisconsin, Madison; the V.I.S.I.O.N. Clinical Trial Group — R. Guymer, S. Quereshi, Centre for Eye Research Australia, East Melbourne, Australia; I. Constable, Lions Eye Institute, Nedlands, Australia; J. Arnold, S. Sarks, Marsden Eye Specialists, Parramatta, Australia; A. Chang, Eye and Vision Research Institute, Sydney; M. Gillies, Save Sight Institute, Sydney; P. Mitchell, Westmead Hospital, Westmead, Australia; A. Haas, Universitäts Augenklinik, Graz, Austria; M. Stur, Augenklinik Abt, Vienna; A. Leys, UZ St. Rafaël, Leuven, Belgium; C. Moreira, E. Portella, Hospital de Olhos do Paraná, Curitiba, Brazil; M. de Avila, A.C. Taleb, Universidade Federal de Goiás, Goiânia, Brazil; J. Lavinsky, Hospital das Clínicas de Porto Alegre, Porto Alegre, Brazil; M.E. Farah, Universidade Federal de São Paulo, São Paulo; G. Williams, Calgary Retina Consultants, Calgary, Alta., Canada; B. Leonard, University of Ottawa Eye Institute, Ottawa; R. Garcia, Eye Centre Pasqua Hospital, Regina, Sask., Canada; D. Maberley, Vancouver Hospital and Health Sciences Center, University of British Columbia Eye Care Center, Vancouver, Canada; J.M. Lopez, Pontificia Universidad Católica de Chile, Santiago, Chile; F. Rodriguez, Fundación Oftalmologico Nacional, Bogotá, Colombia; I. Fiser, Vinohrady Teaching Hospital, Prague, Czech Republic; M. Larsen, Herlev Hospital, Herlev, Denmark; J.-F. Korobelnik, Groupe Hospitalier Pellegrin, Bordeaux, France; G. Soubrane, Hospitalier Universitaire de Creteil, Creteil, France; F. Koenig, Centre de Recherche en Ophtalmologie, Lyon, France; A. Gaudric, Hopital Lariboisiere, Paris; S. Dithmar, F.G. Holz, University of Heidelberg, Heidelberg, Germany; A. Joussen, B. Kirchhof, University of Cologne, Cologne, Germany; P. Wiedemann, Universitätsklinikum Leipzig Klinik und Poliklinik, Leipzig, Germany; D. Pauleikhoff, St. Franziskus Hospital, Muenster, Germany; U. Schneider, University Eye Clinic Tübingen, Tübingen, Germany; I. Suveges, Semmelweis University, Budapest, Hungary; J. Gyory, Csolnoky Ferenc County Hospital, Kórház, Hungary; A. Pollack, Kaplan Medical Center, Rehovot, Israel; A. Loewenstein, Ichilov Medical Center, Tel Aviv, Israel; I. Rosenblatt, Rabin Medical Center, Tikva, Israel; A. Giovannini, Istituto di Scienze Oftalmologiche, Ancona, Italy; U. Menchini, II Clinica Oculistica Universitá degli Studi di Firenze, Firenze, Italy; R. Brancato, Universitario Ospedale San Raffaele,

Milan, Italy; F. Cardillo Piccolino, F.M. Grignolo, Università di Torino, Turin, Italy; F. Bandello, Policlinico Universitario, Udine, Italy; R. Schlingemann, AMC University of Amsterdam, Amsterdam; A. Deutman, UMC St. Radboud, Institute of Ophthalmology, Nijmegen, the Netherlands; J. Kaluzny, Akademia Medyczna ul M. Sklodowskiej-Curie, Bydgoszcz, Poland; K. Pecold, Akademia Medyczna ul. Dluga, Poznań, Poland; J. Cunha-Vaz, R. da Silva, Associacão Para Investigacão Biomedica e Inovacão Em Luz e Imagem, Universidada de Coimbra, Coimbra, Portugal; J.M. Ruiz Moreno, VISSUM-Instituto Oftalmologico de Alicante, Alicante, Spain; J. Mones, Instituto de Microcirugia Ocular, Barcelona, Spain; M. Figueroa, Hospital Oftalmologico Internacional, Madrid; C. Pournaras, Hopital Cantonal de Geneva, Geneva; L. Zografos, Hopital Opthalmique Jules Gonin, Lausanne, Switzerland; N. Lois, Aberdeen Royal Infirmary, Aberdeen, United Kingdom; U. Chakravarthy, Queen's University Belfast Royal Victoria Hospital, Belfast, United Kingdom; P. Hykin, Moorfields Eye Hospital, London; I. Chisholm, Southampton General Hospital, Southampton, United Kingdom; M.W. Johnson, W.K. Kellogg Eye Center, Ann Arbor, Mich.; D. Marcus, Medical College of Georgia, Augusta; N. Mandava, Rocky Mountain Lion Eye Institute, Aurora, Ill.; J. Haller, Wilmer Eye Institute, Baltimore; F. Cangemi, Vitreo-Retinal Associates of New Jersey, Belleville; D. Boyer, Retina Vitreous Associates, Beverly Hills, Calif.; J. Arroyo, J. Lowenstein, Massachusetts Eye and Ear Infirmary, Boston; J. Heier, Ophthalmic Consultants of Boston, Boston; E. Reichel, New England Eye Center, Boston; P.M. Falcone, Connecticut Retina Consultants, Bridgeport; D.J. Weissgold, University of Vermont College of Medicine, Burlington; B.P. Conway, University of Virginia, Charlottesville; R. Garfinkel, Retina Group of Washington, Chevy Chase, Md., B. Glaser, Glaser Murphy Retina Treatment Centers, Chevy Chase, Md.; A.T. Lyon, D. Weinberg, Northwestern University Sorrel Rosin Eye Center, Chicago; H. Lewis, Cleveland Clinic Cole Eye Institute, Cleveland; J.A. Wells, Palmetto Retina Center, Columbia, S.C.; L. Wilcox, Eye Center of Concord, Concord, N.H.; G. Fish, Texas Retina Associates, Dallas; D. Eliot, Kresge Eye Institute, Detroit; S. Fekrat, Duke University Eye Center, Durham, N.C.; B. Taney, Retina Vitreous Consultants, Fort Lauderdale, Fla.; A.M. Eaton, Retina Health Center, Fort Myers, Fla.; V. Deramo, S. Harrison, L.I. Vitreo-Retinal Consultants, Great Neck, N.Y.; J. Wroblewski, Cumberland Valley Retina Center, Hagerstown, Md.; D. Tom, New England Retina Associates, Hamden, Conn.; D.H. Chow, Illinois Retina Associates, Harvey; E. Holz, W. Mieler, Baylor College of Medicine, Houston; B. Kuppermann, University of California, Irvine; N. Sabates, Eye Foundation of Kansas City, Kansas City, Mo.; H. Cummings, Southeastern Retina Associates, Knoxville, Tenn.; S.D. Pendergast, Retina Associates of Cleveland, Lakewood, Ohio; C. Gonzales, Jules Stein Eye Institute, Los Angeles; J. Lim, Doheny Eye Institute, Los Angeles; S. Charles, Charles Retina Institute, Memphis, Tenn.; S. Sanislo, Stanford University School of Medicine, Menlo Park, Calif.; P. Rosenfeld, Bascom Palmer Eye Institute, Miami; T. Connor, Eye Institute, Milwaukee; H. Cantrill, VitreoRetinal Surgery, Minneapolis; R.D. Ross; R. Willson, Foundation for Retinal Research, New Orleans; K. Bailey-Freund, Manhattan Eye, Ear & Throat Retinal Research Office, New York; R. Rosen, New York Eye and Ear Infirmary, New York; R. Leonard, S. Nanda, Dean A. McGee Eye Institute, Oklahoma City; A. Brucker, Scheie Eye Institute, Philadelphia; A. Ho, Wills Eye Hospital Retina Research, Philadelphia; S. Sneed, Retinal Consultants of Arizona, Phoenix; T. Friberg, Eye and Ear Institute, Pittsburgh; M. Klein, Casey Eye Institute, Portland, Oreg.; P. Tornambe, Retina Consultants, Poway, Calif.; G. Stoller, Ophthalmic Consultants of Long Island, Rockville Centre, N.Y.; A. Capone, Associated Retinal Consultants, Royal Oak, Mich.; P. Bernstein, John Moran Eye Center, University of Utah, Salt Lake City; H.R. McDonald, H. Schatz, R.N. Johnson, West Coast Retina Medical Group, San Francisco; M. Nanda, Orange County Retina, Santa Ana, Calif.; R. Avery, California Retina Consultants, Santa Barbara; K. Wong, Sarasota Retina Institute, Sarasota, Fla.; W.S. Grizzard, Retina Associates of Florida, Tampa; P. Higgins, Retina Associates of New Jersey, Teaneck; H. Hudson, L. Joffe, Retina Associates, Tucson, Ariz.; M. Varenhorst, Vitreo-Retinal Consultants and Surgeons, Wichita, Kans.; M.M. Slusher, Wake Forest University Eye Center, Winston-Salem, N.C; A.P. Adamis, F. Betts, E.T. Cunningham, Jr., K. Curtiss, M. Feinsod, D. Guyer, E. Harrison, H. Masonson, D. O'Shaughnessy, Eyetech Pharmaceuticals, New York; C. Beals, D. Eveleth, K. Ludwig, M. Patel, Pfizer, New York.

REFERENCES

1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971;285:1182-6.
2. Adamis AP, Miller JW, Bernal M-T, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am J Ophthalmol 1994;118:445-50.
3. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480-7.
4. Malecaze F, Clamens S, Simorre-Pinatel V, et al. Detection of vascular endothelial growth factor messenger RNA and vascular endothelial growth factor-like activity in proliferative diabetic retinopathy. Arch Ophthalmol 1994;112:1476-82.
5. Amano S, Rohan R, Kuroki M, Tolentino M, Adamis AP. Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization. Invest Ophthalmol Vis Sci 1998;39:18-22.
6. Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol 1996;114:66-71.
7. Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proc Natl Acad Sci U S A 1995;92:10457-61.
8. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002;120:338-46.
9. Leung DW, Cachianes G, Kuang W-J, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246:1306-9.
10. Tolentino MJ, McLeod DS, Taomoto M, Otsuji T, Adamis AP, Lutty GA. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. Am J Ophthalmol 2002;133:373-85.
11. Tolentino MJ, Miller JW, Gragoudas ES, Chatzistefanou K, Ferrara N, Adamis AP. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. Arch Ophthalmol 1996;114:964-70.
12. Schwesinger C, Yee C, Rohan RM, et al. Intrachoroidal neovascularization in transgenic mice overexpressing vascular endothelial growth factor in the retinal pigment epithelium. Am J Pathol 2001;158:1161-72.
13. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477-85.
14. Ferris FL III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 1984;102:1640-2.
15. Bressler NM, Bressler SB, Congdon NG, et al. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. Arch Ophthalmol 2003;121:1621-4.
16. Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol 1967;63:Suppl:S1-S139.
17. Green WR. Histopathology of age-related macular degeneration. Mol Vis 1999;5:27-36.
18. Green WR, Enger C. Age-related macular degeneration histopathologic studies:

the 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993;100:1519-35.
19. Dong LM, Childs AL, Mangione CM, et al. Health- and vision-related quality of life among patients with choroidal neovascularization secondary to age-related macular degeneration at enrollment in randomized trials of submacular surgery: SST report no. 4. Am J Ophthalmol 2004;138:91-108.
20. Ruckman J, Green LS, Beeson J, et al. 2′-Fluoropyrimidine RNA-based aptamers to the 165-amino acid form of vascular endothelial growth factor ($VEGF_{165}$): inhibition of receptor binding and VEGF-induced vascular permeability through interactions requiring the exon 7–encoded domain. J Biol Chem 1998;273:20556-67.
21. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials — TAP report. Arch Ophthalmol 1999; 117:1329-45.
22. Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreous injection: a comprehensive review. Retina 2004;24: 676-98.
23. Aiello LP, Brucker AJ, Chang S, et al. Evolving guidelines for intravitreous injections. Retina 2004;24:Suppl:S3-S19.
24. Ishida S, Usui T, Yamashiro K, et al. VEGF164 is proinflammatory in the diabetic retina. Invest Ophthalmol Vis Sci 2003;44: 2155-62.

May 08, 2008

Bayer and Regeneron start additional Phase 3 Study for VEGF Trap-Eye in Wet Age-related Macular Degeneration

International study to evaluate efficacy and safety in treating a leading cause of blindness

Leverkusen, Germany, Montville, NJ and Tarrytown, NY, May 8, 2008 - Bayer HealthCare AG and development partner Regeneron Pharmaceuticals, Inc. (NASDAQ:REGN) today announced that the first patient has been dosed in the new VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of the neovascular form of age-related macular degeneration (wet AMD), a leading cause of blindness in adults.

VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) will enroll approximately 1,200 patients in up to 200 centers in Europe, Asia Pacific, Japan and Latin America. The first Phase 3 trial, VIEW 1, began enrolling patients in August 2007 in the United States and Canada. Both VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks. The development program will include visual acuity endpoints and anatomical endpoints, including retinal thickness, a measure of disease activity. The trial is intended to establish

non-inferiority of VEGF Trap-Eye with Lucentis® (ranibizumab) an antiangiogenic agent approved for use in wet AMD in major markets globally.

Wet AMD accounts for about 90 percent of all severe AMD-related vision loss. It occurs when abnormal blood vessels in the eye leak fluid and blood into the macula, the area of the retina that allows for vision of fine details. This can lead to a rapid loss of central vision with continued progression.

"Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision," said Kemal Malik, MD, Head of Global Development and member of the Bayer HealthCare Executive Committee. "Dosing of the first patient in this confirmatory Phase 3 trial is an important milestone for this compound intended to treat a devastating ocular disease that impacts millions of people worldwide."

"New therapies are still needed to provide optimal care to those patients with wet AMD," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "This global Phase 3 clinical program will provide additional data to further evaluate the efficacy and safety of VEGF Trap-Eye using different dosing regimens."

Bayer HealthCare and Regeneron are collaborating on the global development of VEGF Trap-Eye for treatment of wet AMD, diabetic eye diseases, and other ocular diseases and disorders. Once approved, Bayer HealthCare will market VEGF Trap-Eye outside the U.S., where the parties will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the U.S. VIEW 2 primary analysis results are anticipated in 2011.

About VIEW 2
In the first year, the VIEW 2 study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every 4 weeks. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-

based extended regimen with a dose administered at least every 12 weeks, but not more often than every 4 weeks until the end of the study.

The primary endpoint of the study is the proportion of patients treated with VEGF Trap-Eye who maintain vision at the end of one year, compared to ranibizumab patients. Visual acuity is defined as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, a standard chart used in research to measure visual acuity. Maintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart. Key secondary endpoints include the mean change from baseline in visual acuity as measured by ETDRS and the proportion of patients who gained at least 15 letters of vision at week 52.

Phase 2 Clinical Data

In a Phase 2 trial in 157 patients, announced in October 2007 at the Retina Society Conference in Boston, VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart).

About VEGF Trap-Eye

Vascular endothelial growth factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger the formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye, which lead to the development of wet AMD. VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PlGF) and VEGF-B. VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. Blockade of VEGF can prevent abnormal blood vessel formation as well as vascular leak and has proven beneficial in the treatment of wet AMD.

About Wet AMD

Age-related macular degeneration (AMD) is a leading cause of acquired

blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subsidiary of Bayer AG, is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Diabetes Care and Pharmaceuticals divisions. The pharmaceuticals business operates under the name Bayer Schering Pharma AG. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Find more information at **www.bayerhealthcare.com**.

Bayer Schering Pharma is a worldwide leading specialty pharmaceutical company. Its research and business activities are focused on the following areas: Diagnostic Imaging, General Medicine, Specialty Medicine and Women's Healthcare. With innovative products, Bayer Schering Pharma aims for leading positions in specialized markets worldwide. Using new ideas, Bayer Schering Pharma aims to make a contribution to medical progress and strives to improve the quality of life. Find more information at **www.bayerscheringpharma.de**.

About Regeneron

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYSTTM (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, and inflammatory diseases, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's Web site at **www.regeneron.com**.

(Note: Lucentis® is a registered trademark of Genentech, Inc.)

Forward-looking statements
Bayer HealthCare This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at **www.bayer.com**. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Regeneron This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-Q for the quarter ended March 31, 2008. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise

unless required by law.

27. Februar 2019 16:01 Uhr MEZ

70,03

5,31 %

27. Februar 2019 15:56 Uhr MEZ

11.508,14

-0,28 %

Services

Please choose

Download

Investor News

Download PDF

collect (69 KB)

Last updated: November 05, 2013

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Intravitreal Aflibercept for Diabetic Macular Edema

148-Week Results from the VISTA and VIVID Studies

Jeffrey S. Heier, MD,[1] Jean-François Korobelnik, MD,[2,3,4] David M. Brown, MD,[5] Ursula Schmidt-Erfurth, MD,[6] Diana V. Do, MD,[7] Edoardo Midena, MD,[8] David S. Boyer, MD,[9] Hiroko Terasaki, MD,[10] Peter K. Kaiser, MD,[11] Dennis M. Marcus, MD,[12] Quan D. Nguyen, MD,[7] Glenn J. Jaffe, MD,[13] Jason S. Slakter, MD,[14] Christian Simader, MD,[6] Yuhwen Soo, PhD,[15] Thomas Schmelter, PhD,[16] Robert Vitti, MD,[15] Alyson J. Berliner, MD, PhD,[15] Oliver Zeitz, MD,[16,17] Carola Metzig, MD,[16] Frank G. Holz, MD[18]

Purpose: To compare efficacy and safety of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME) over 3 years.

Design: Two similarly designed phase 3 trials: VISTA^{DME} and VIVID^{DME}.

Participants: Patients (eyes; n = 872) with central-involved DME.

Methods: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control. From week 24, if rescue treatment criteria were met, IAI patients received active laser, and laser control patients received IAI 2q8. From week 100, laser control patients who had not received IAI rescue treatment received IAI as needed per retreatment criteria.

Main Outcome Measures: The primary end point was the change from baseline in best-corrected visual acuity (BCVA) at week 52. We report the 148-week results.

Results: Mean BCVA gain from baseline to week 148 with IAI 2q4, IAI 2q8, and laser control was 10.4, 10.5, and 1.4 letters ($P < 0.0001$) in VISTA and 10.3, 11.7, and 1.6 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained ≥15 letters from baseline at week 148 was 42.9%, 35.8%, and 13.6% ($P < 0.0001$) in VISTA and 41.2%, 42.2%, and 18.9% ($P < 0.0001$) in VIVID, respectively. Greater proportions of eyes treated with IAI 2q4 and IAI 2q8 versus those treated with laser control had an improvement of ≥2 steps in the Diabetic Retinopathy Severity Scale (DRSS) score in both VISTA (29.9% and 34.4% vs. 20.1% [$P = 0.0350$, IAI 2q4; $P = 0.0052$, IAI 2q8]) and VIVID (44.3% and 47.8% vs. 17.4% [$P < 0.0001$ for both]). In an integrated safety analysis, the most frequent ocular serious adverse event was cataract (3.1%, 2.1%, 0.3% for 2q4, 2q8, and control).

Conclusions: Visual improvements observed with both IAI regimens (over laser control) at weeks 52 and 100 were maintained at week 148, with similar overall efficacy in the IAI 2q4 and IAI 2q8 groups. Treatment with IAI also had positive effects on the DRSS score. Over 148 weeks, the incidence of adverse events was consistent with the known safety profile of IAI. *Ophthalmology 2016;■:1–10 © 2016 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

The diabetes mellitus epidemic is growing. According to current predictions, by 2040, approximately 1 in every 10 adults (642 million) worldwide will have the disease.[1] Diabetic retinopathy and associated diabetic macular edema (DME) are serious diabetes mellitus complications and are the leading causes of blindness and visual disability in working-age adults.[2,3]

Current treatment options for DME include macular laser photocoagulation,[4] corticosteroids,[5] and anti-vascular endothelial growth factor (VEGF) agents (i.e., intravitreal aflibercept, ranibizumab, and off-label use of bevacizumab).[6–8] There is a large body of evidence to support anti-VEGF use. Because of superior anatomic and functional outcomes,[6–11] anti-VEGF agents have rapidly replaced macular laser photocoagulation as the standard of care to treat DME.

Aflibercept, a 115-kDA recombinant fusion protein, is composed of the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the constant Fc domain of human immunoglobulin G1,[12] and it binds VEGF-A with high affinity.[13] Unlike ranibizumab and bevacizumab, aflibercept also binds to placental growth factor.[13] Intravitreal aflibercept injection (IAI), which is also known as "VEGF Trap Eye" or "IVT-AFL" in the scientific literature, is currently indicated to treat neovascular age-related macular degeneration (AMD), macular edema

http://dx.doi.org/10.1016/j.ophtha.2016.07.032
ISSN 0161-6420/16

VEGF Trap-Eye in Wet AMD
CLEAR-IT 2: One-Year Key Results

A Phase 2, Randomized, Controlled Dose- and Interval-Ranging Study of Intravitreal VEGF Trap-Eye in Patients With Neovascular, Age-Related Macular Degeneration

CLEAR-IT 2: Rationale

- Anti-VEGF therapy has dramatically changed the treatment paradigm for wet AMD
  - Improvement in visual acuity is now an achievable goal of treatment
- A potential limitation of anti-VEGF therapy is the unpredictable durability of vision gain initially achieved with monthly dosing when the treatment interval is prolonged
- VEGF Trap-Eye is a novel anti-VEGF therapy with high binding affinity for VEGF-A and placental growth factor (PlGF)
- CLEAR-IT 2 was designed to assess:
  - Response at 12 weeks to a range of doses administered monthly and quarterly
  - Durability of response with PRN (as-needed) dosing out to 1 year

CLEAR-IT 2: Study Design

Randomized, multicenter, double-masked trial
N=159

Subjects randomized 1:1:1:1:1

0.5 mg q4 wks	2 mg q4 wks	0.5 mg q12 wks	2 mg q12 wks	4 mg q12 wks
n=32	n=32	n=32	n=32	n=31

Primary endpoint: Change in Central Retinal/Lesion Thickness (CR/LT)

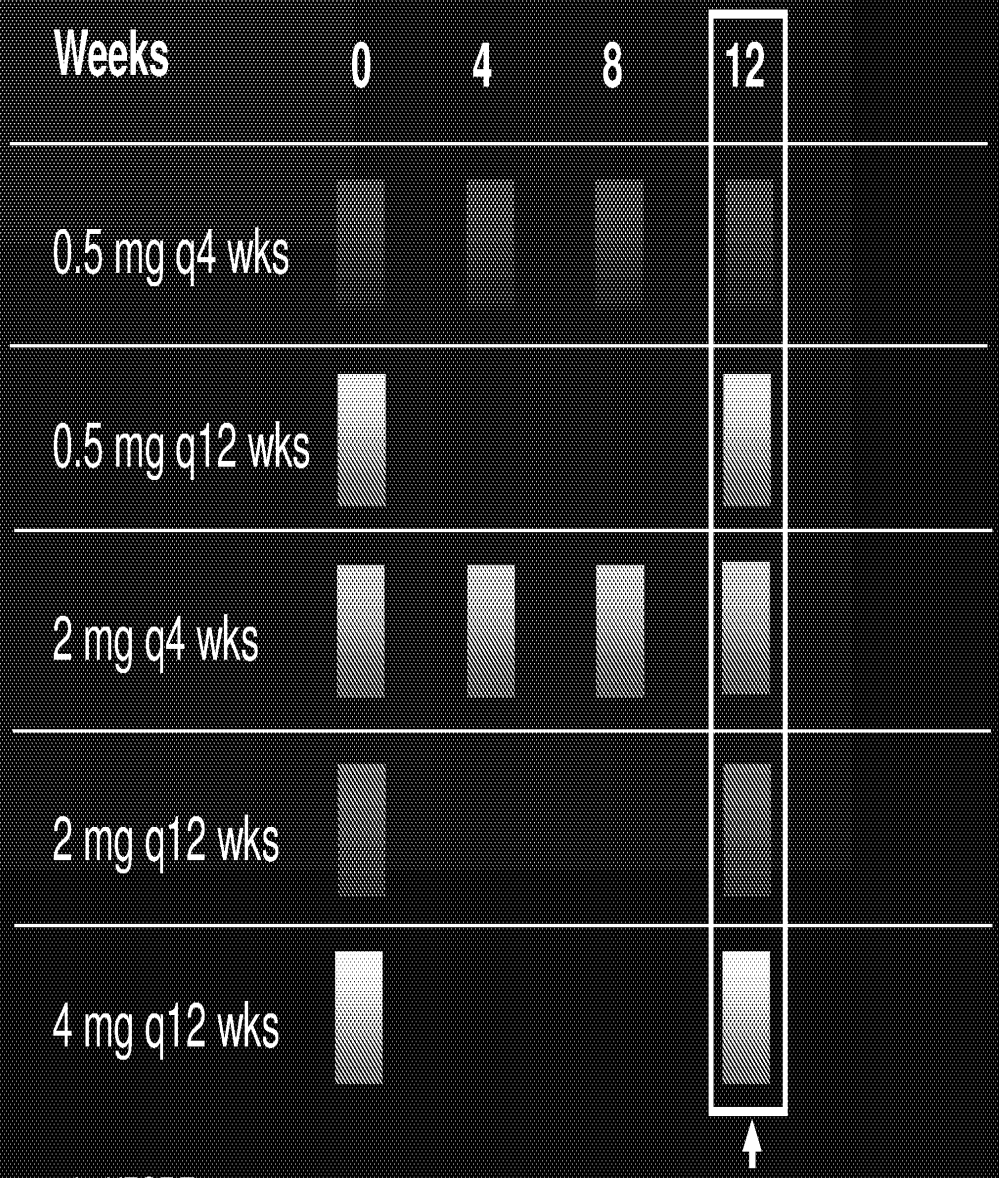
Fixed dosing to week 12 (primary endpoint)

Secondary endpoint: Best-Corrected ETDRS Visual Acuity (BCVA)

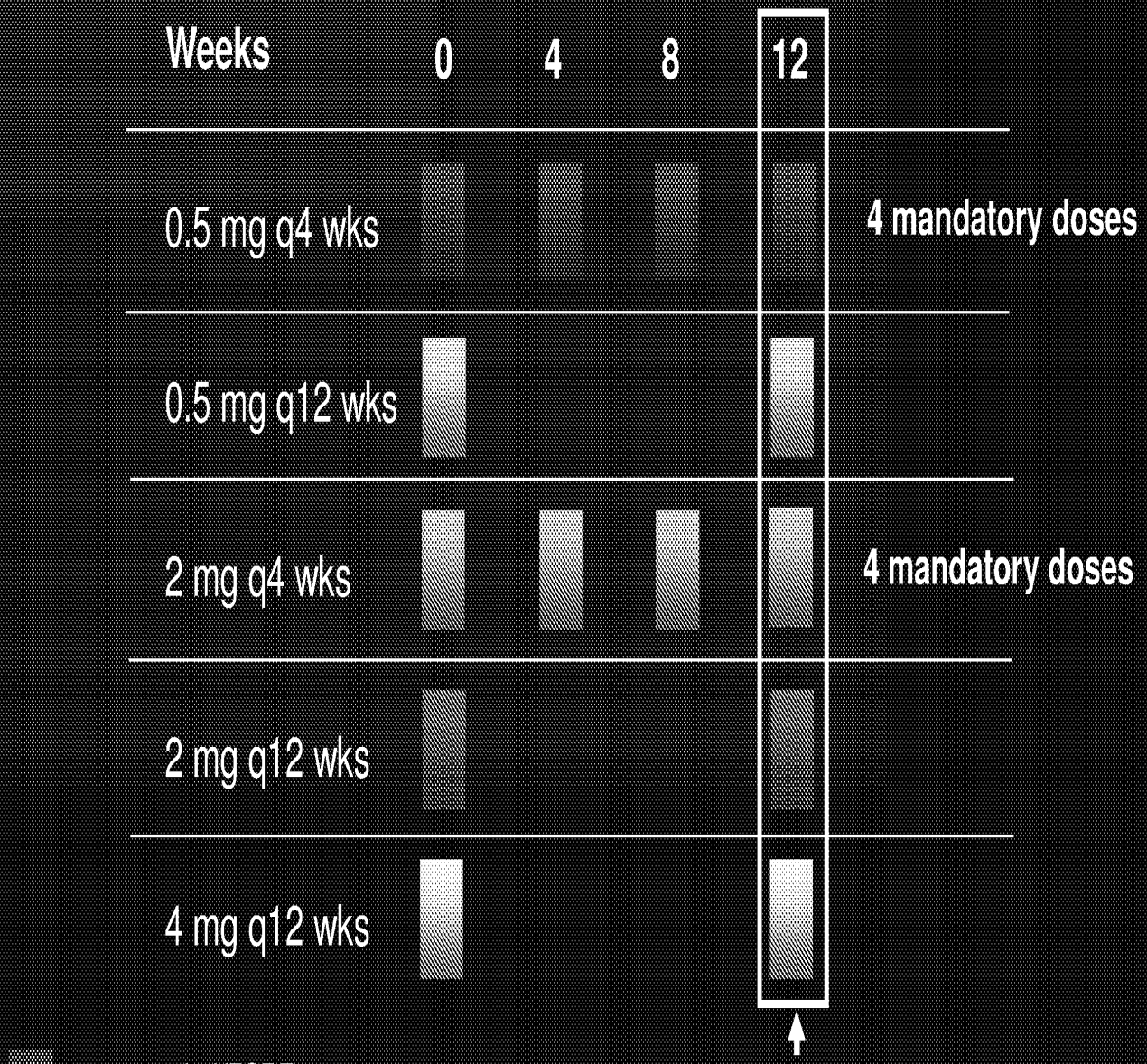
PRN dosing to 1 year

Patients were re-dosed at week 12; PRN dosing started at week 16

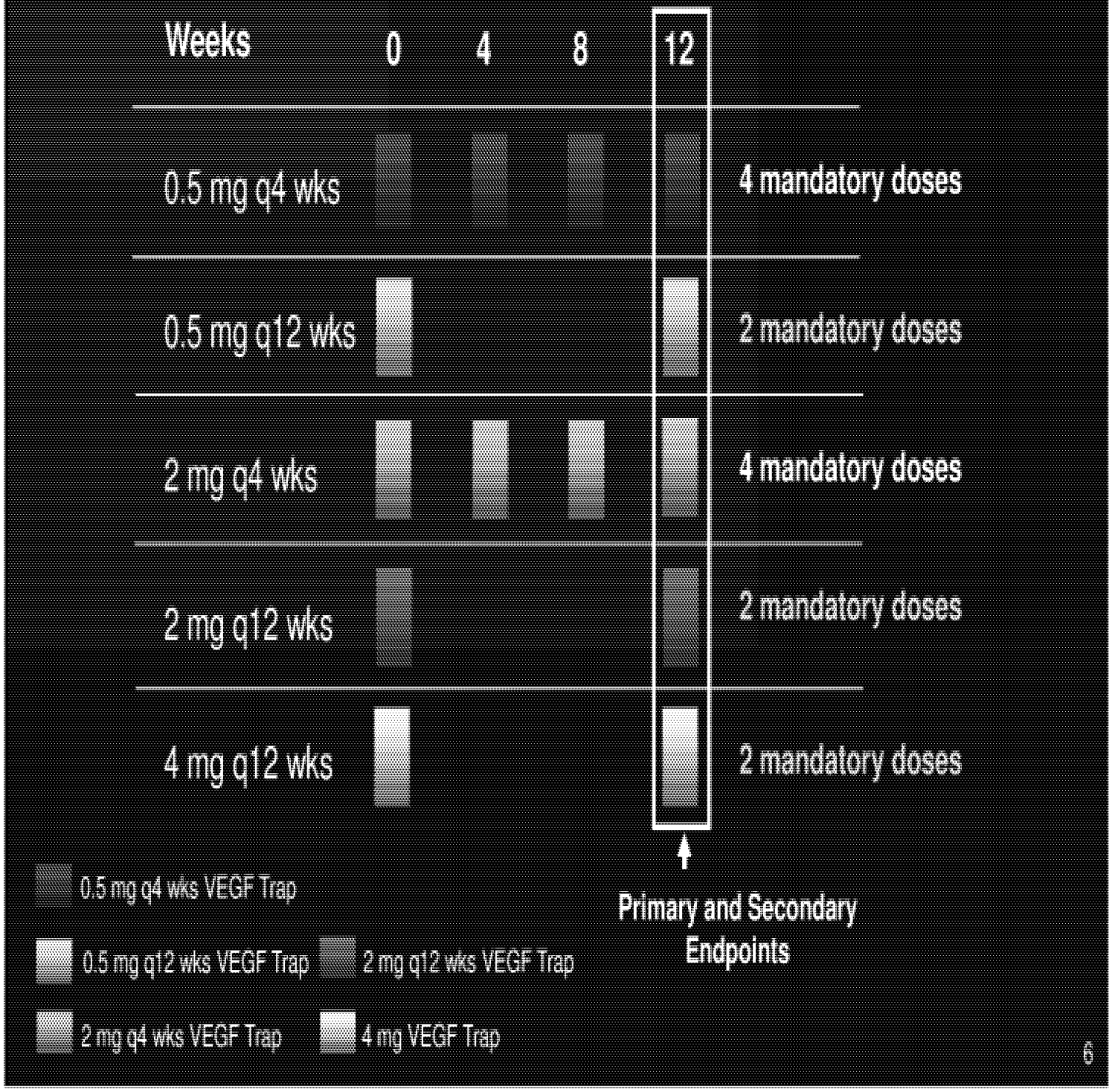
Study Schedule
(fixed-dosing phase)



Study Schedule
(fixed-dosing phase)



Study Schedule
(fixed-dosing phase)



Baseline Characteristics

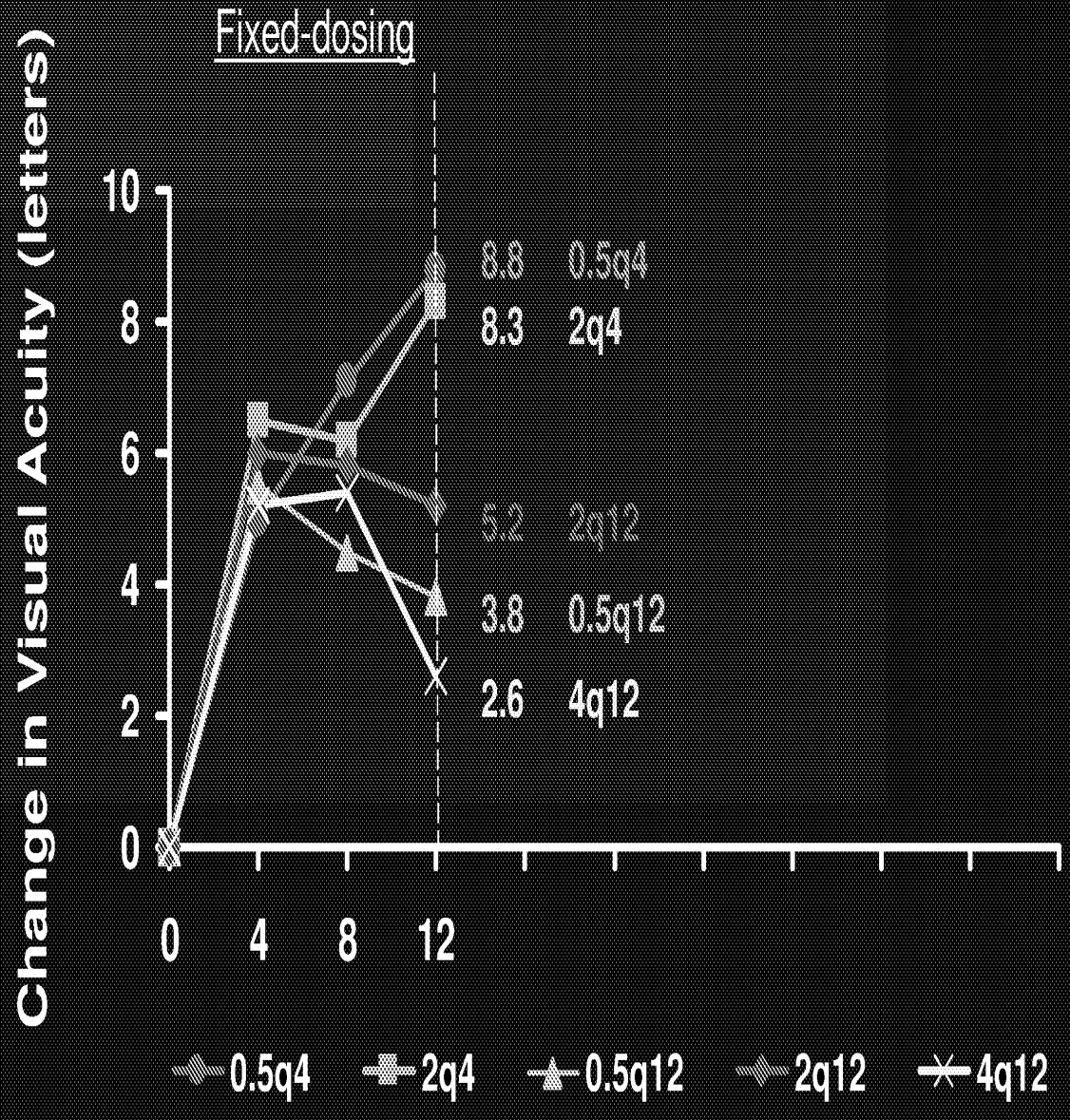
(n=157*)	Mean	Range
Age (years)	78.2	53-94
Gender (% M:% F)	38:62	
Disease Duration (months)	3.9	0-67
Lesion Size (mean±SD) in disc areas	3.11±2.12	
Lesion Type: number (%)		
Classic	30 (19.1)	
Predominantly Classic	30 (19.1)	
Minimally Classic	37 (23.6)	
Occult Lesions	60 (38.2)	
Disease Status		
Central Retinal/Lesion Thickness	456 µm	186-1316 µm
Foveal Thickness	327 µm	116-1081 µm
ETDRS BCVA (letters)	56	27-83

*N=159 randomized; n=157 treated

Primary Endpoint Results

Presented at Retina Society 2007

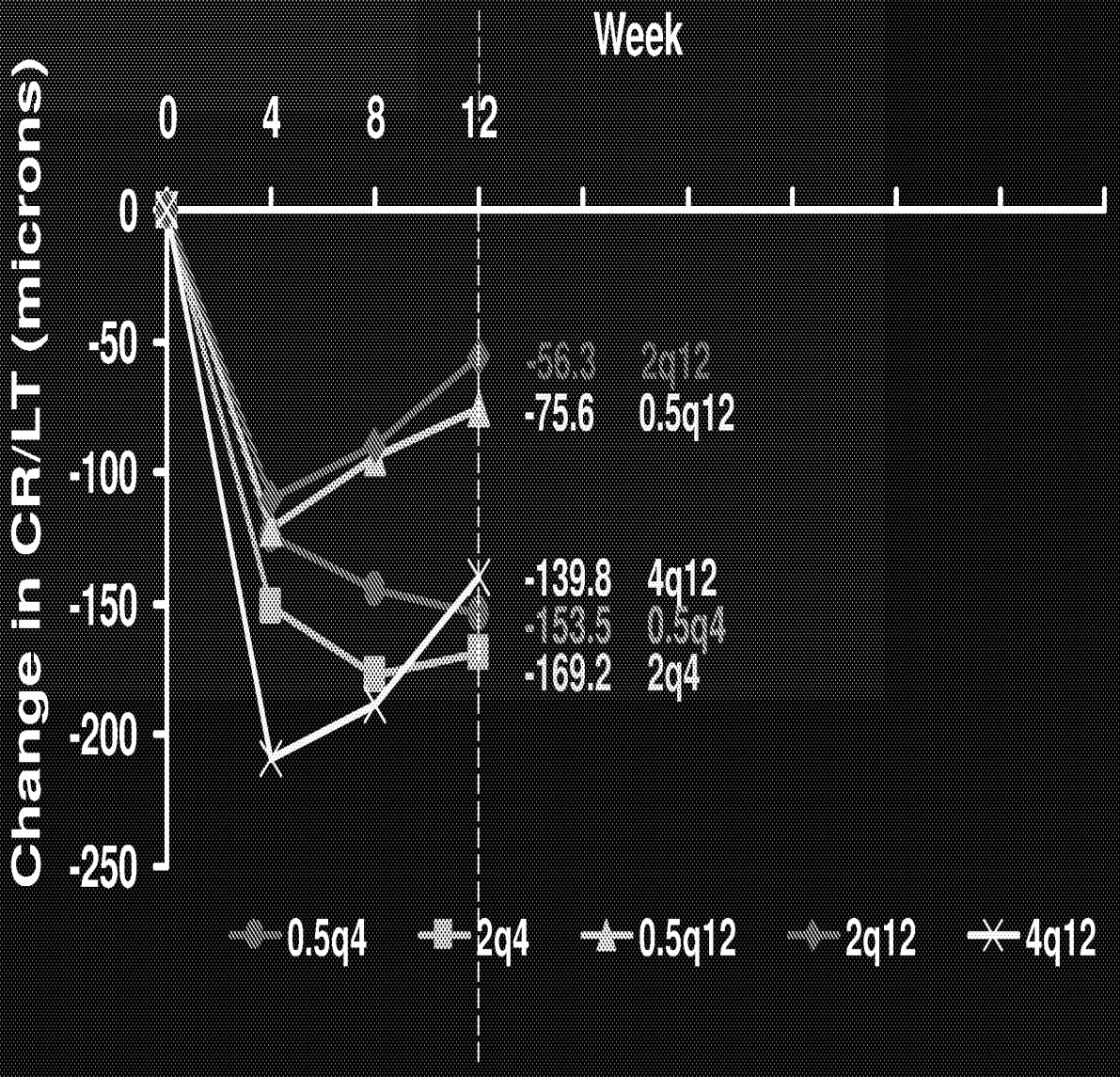
Mean Change in Visual Acuity at 12 Weeks



LOCF analysis; paired t-test; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

Mean Change in Central Retinal/ Lesion Thickness at 12 Weeks

Fixed-dosing



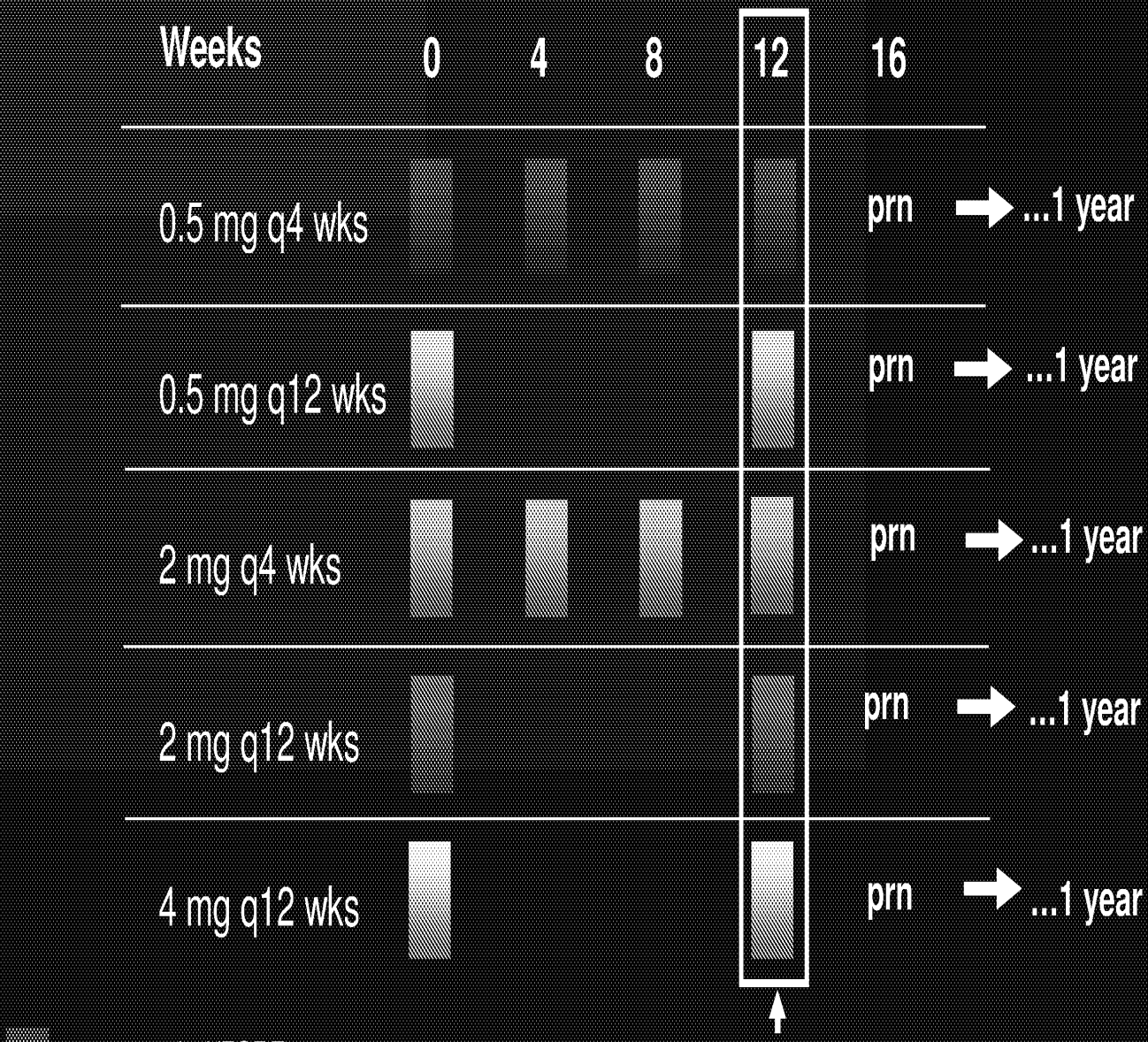
Posterior Pole Scans; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

Primary Endpoint Results: Reported at 2007 Retina Society

At 12 weeks VEGF Trap-Eye:

- Significantly improved mean visual acuity
  - 5.7 letters for all groups combined , $p<0.0001$
- Significantly reduced central retinal thickness
  - -119 µm for all groups combined, $p<0.0001$
- Groups dosed at Baseline and at Week 12 showed improved visual acuity and retinal thickness
  - Effect was not as robust as with monthly dosing
- Maintained effect on visual acuity with a single dose to 8 weeks
- Generally well tolerated with no drug-related serious adverse events

Study Schedule



Patient Disposition

No. of Patients	0.5 q4	0.5 q12	2 q4	2 q12	4 q12	All Patients
Screened						301
Randomized	32	32	32	32	31	159
Treated	32	32	31	31	31	157
Completed Wk 52	26	26	29	27	26	134 (84.3%)
Withdrawn by Wk 52	6	6	2	4	5	23 (14.5%)
Reason for Withdrawal						
Non-compliance					1	1 (0.6%)
Subject request	3			2	1	6 (3.8%)
Adverse event				1		1 (0.6%)
Investigator decision	1	1				2 (1.3%)
Sponsor decision	1	1			1	3 (1.9%)
Lost to follow-up		2	1			3 (1.9%)
Death			1		1	2 (1.3%)
Other	1	2		1	1	5 (3.1%)

Adverse Events
(Study eye, all groups combined ≥ 5%)

Adverse Event	Number (N=157)	Percent (%)
Conjunctival Hemorrhage	60	38.2
Increased IOP (transient post-injection)	29	18.5
Refraction Disorder	25	15.9
Retinal Hemorrhage	23	14.6
Visual Acuity Reduced (patient reported)	21	13.4
Vitreous Detachment	18	11.5
Eye Pain	15	9.6
Vitreous Floaters	14	8.9
Detachment of Retinal Pigment Epithelium	12	7.6
Retinal Edema	10	6.4
Visual Disturbance	9	5.7
Blepharitis	8	5.1
Cataract nuclear	8	5.1
Subretinal Fibrosis	8	5.1

IOP=intraocular pressure

Safety: Serious Adverse Events

Ocular Serious Adverse Events in the study eye:

- 1 case of culture-negative endophthalmitis / uveitis (deemed not related to study drug)

Systemic Serious Adverse Events:

- None deemed to be drug-related
- 2 deaths
  - Pulmonary hypertension (pre-existing condition)
  - Pancreatic carcinoma
- Arterial Thromboembolic Events (ATE's): 1 case of hemorrhagic stroke
  - Subject had a history of prior stroke

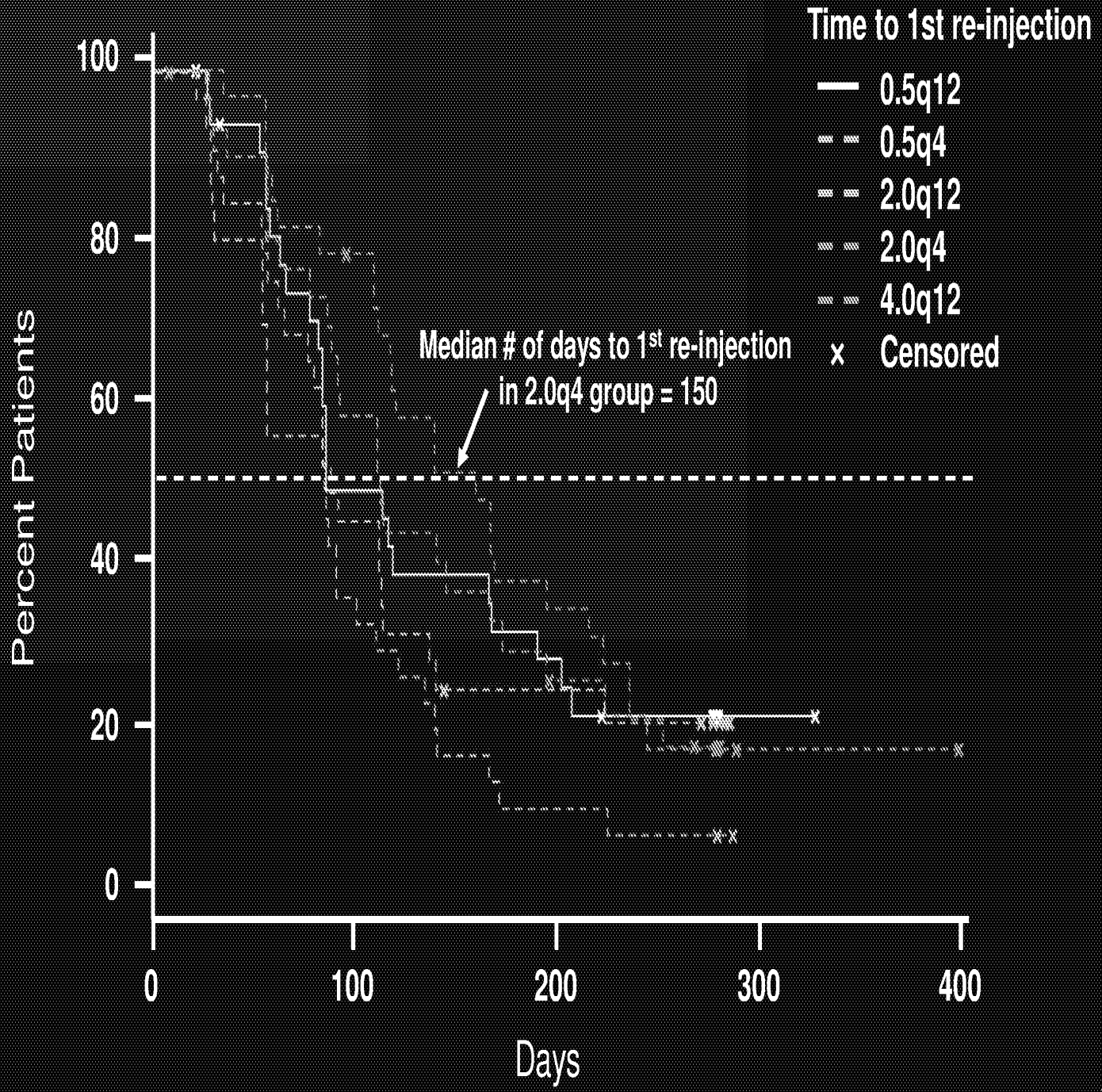
Number of Doses Administered

Re-dosing Criteria (starting at week 16)

- Persistent fluid on OCT
- A loss of ≥ 5 ETDRS letters with recurrent fluid on OCT
- New or persistent leak on FA
- New macular hemorrhage
- Central retinal thickness ≥100μm on OCT
- New onset classic neovascularization

Kaplan-Meier Curve

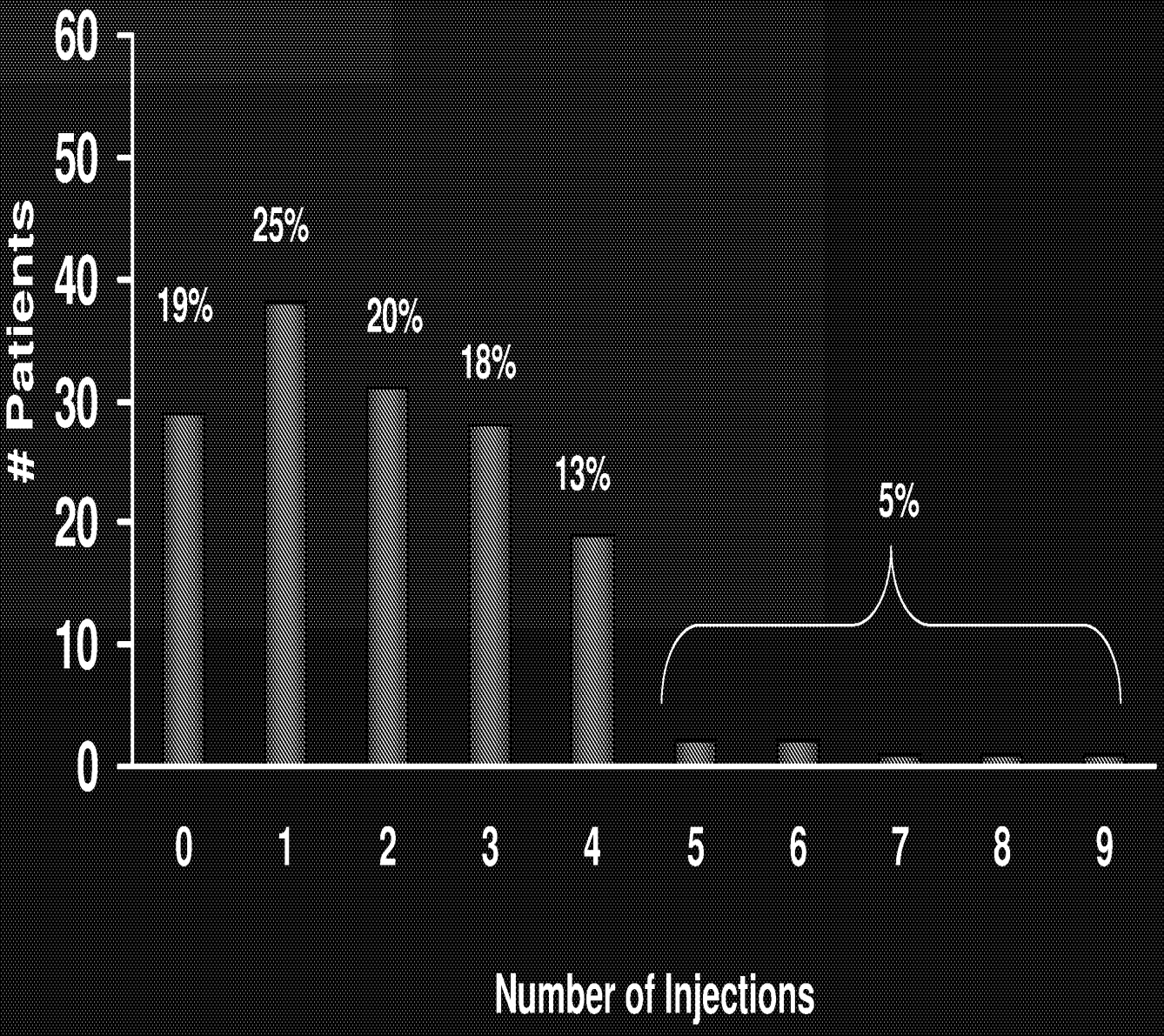
Time to Re-injection (by treatment group)



Re-Treatment Outcome

VEGF Trap-Eye	Mean number of injections over PRN phase (week 12 – 52)	Mean number of days to first injection over PRN phase (week 12 – 52)	Median number of days to first injection over PRN phase (week 12 – 52)
0.5 mg q4	2.52	102	85
2 mg q4	1.55	160	150
0.5 mg q12	1.84	133	86
2 mg q12	2.48	113	86
4 mg q12	1.7	138	111
All	2.01	129	110

Distribution of Injections over PRN Phase
(All groups combined)



Percent of patients receiving an injection analyzed by number of injections, n=152

Re-Treatment Outcome

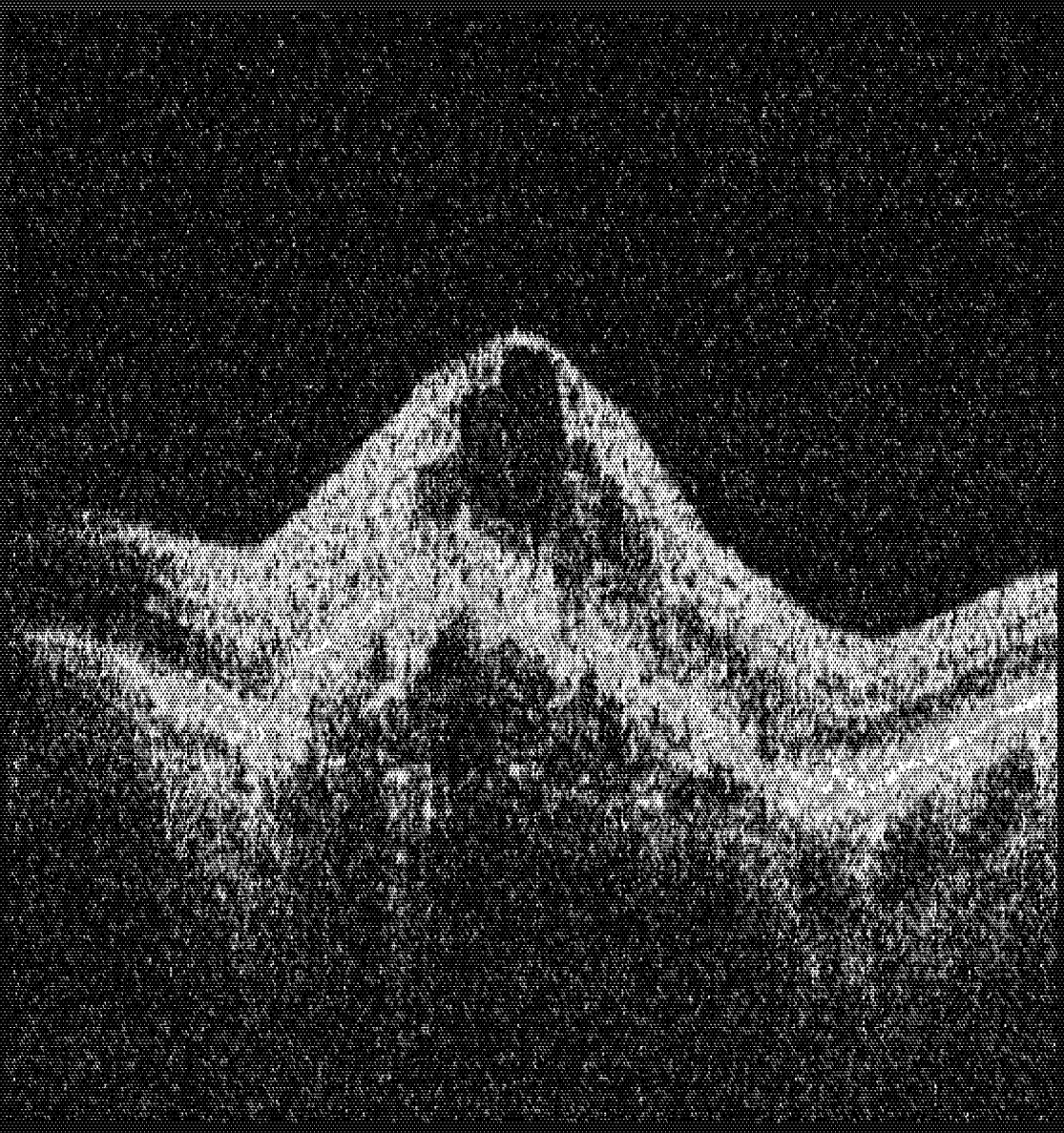
Number of injections over PRN phase*

VEGF Trap-Eye	Mean	Median	Range
0.5 mg q4	2.52	2	0 – 9
2 mg q4	1.55	1	0 – 4
0.5 mg q12	1.84	2	0 – 4
2 mg q12	2.48	3	0 – 5
4 mg q12	1.7	1	0 – 7
All	**2.01**	2	0 – 9

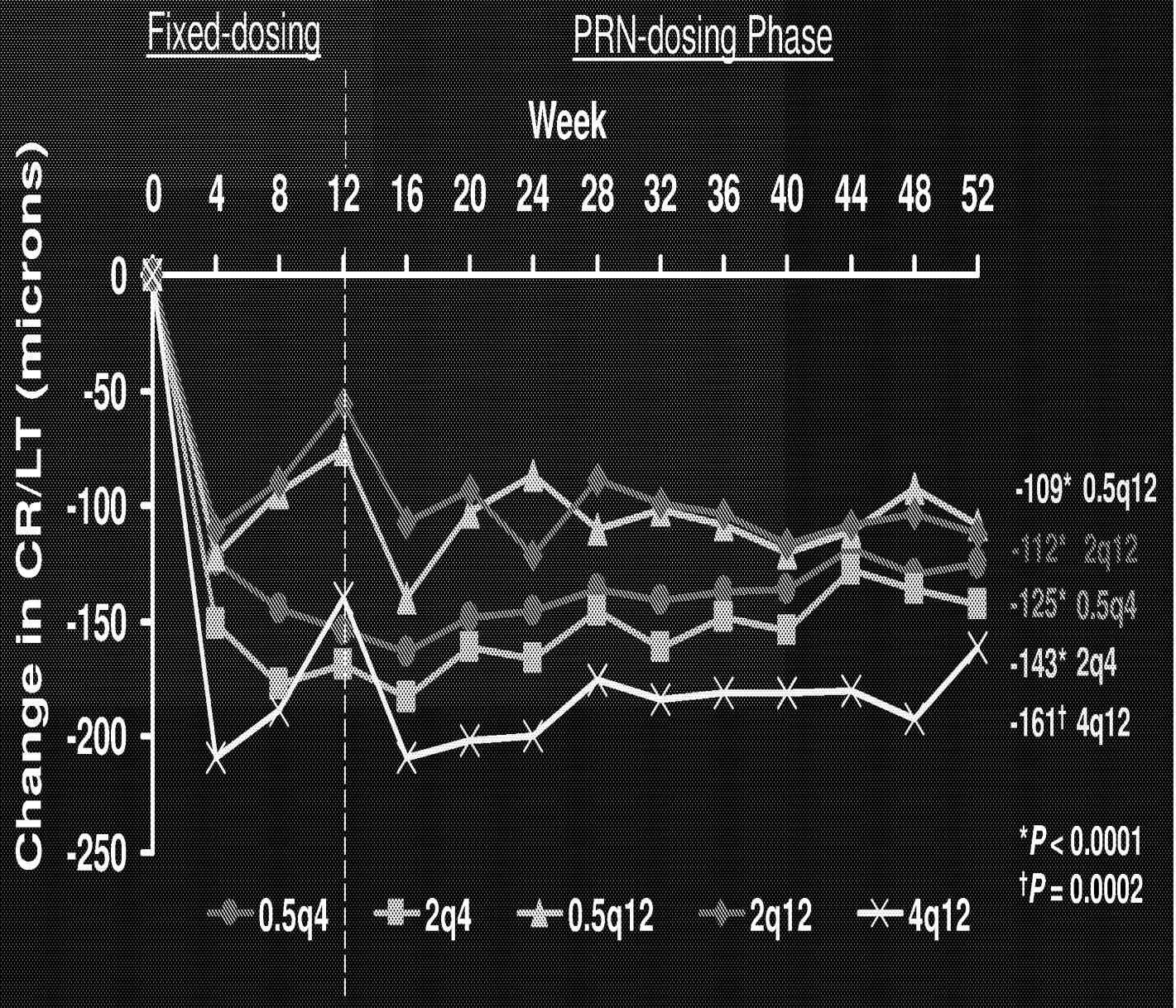
*** After the week 12 injection through week 52**

All patients, n=152

Optical Coherence Tomography

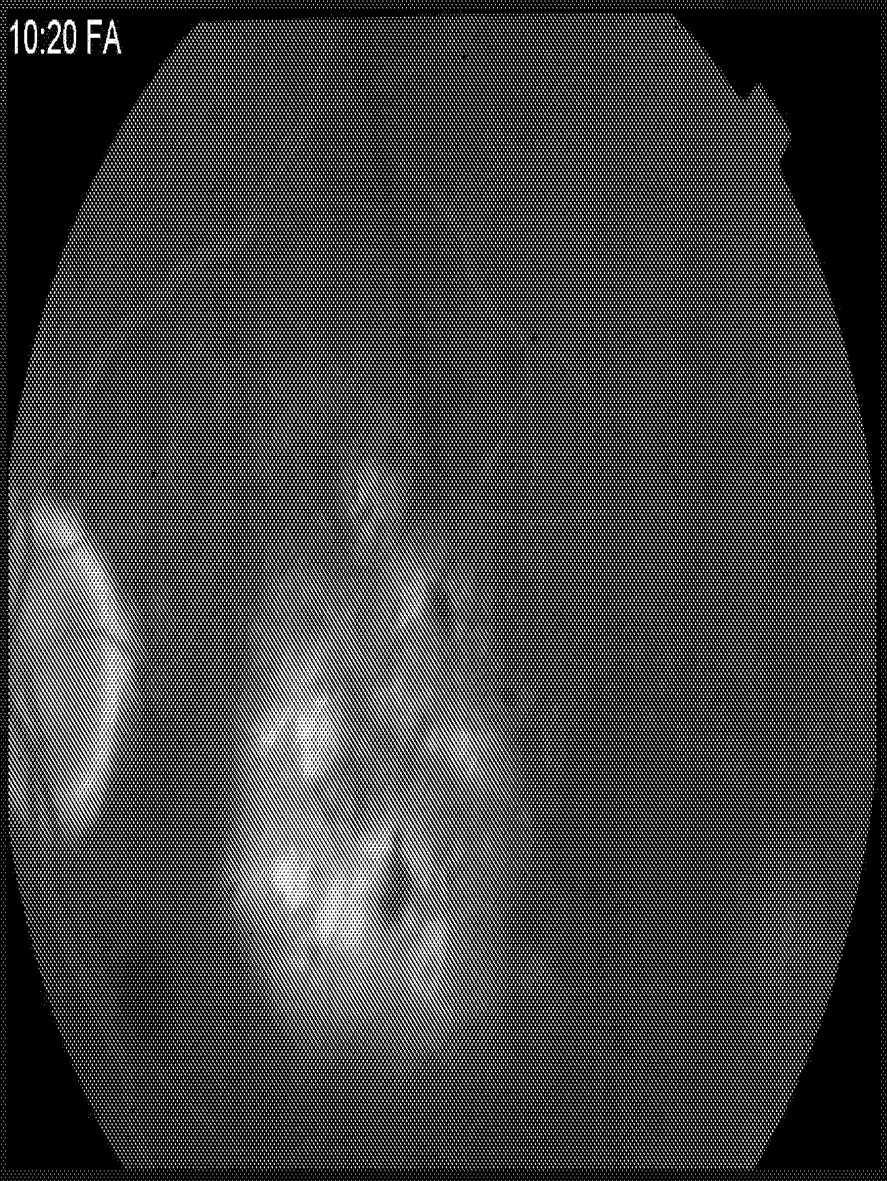


Mean Change in Central Retinal/ Lesion Thickness



Posterior Pole Scans; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

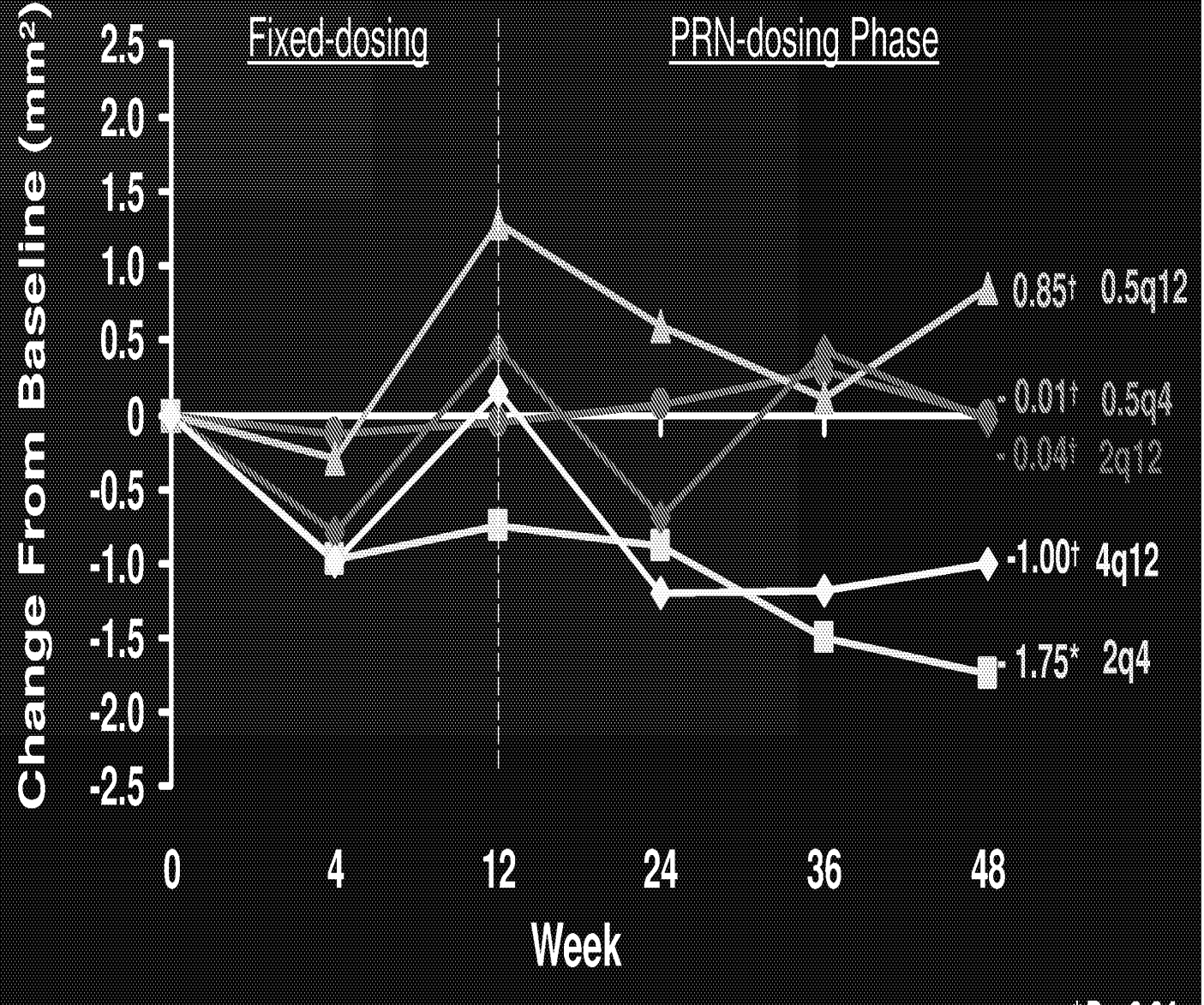
Fluorescein Angiography
1-Year Outcomes



DARC Reading Center: Definitions

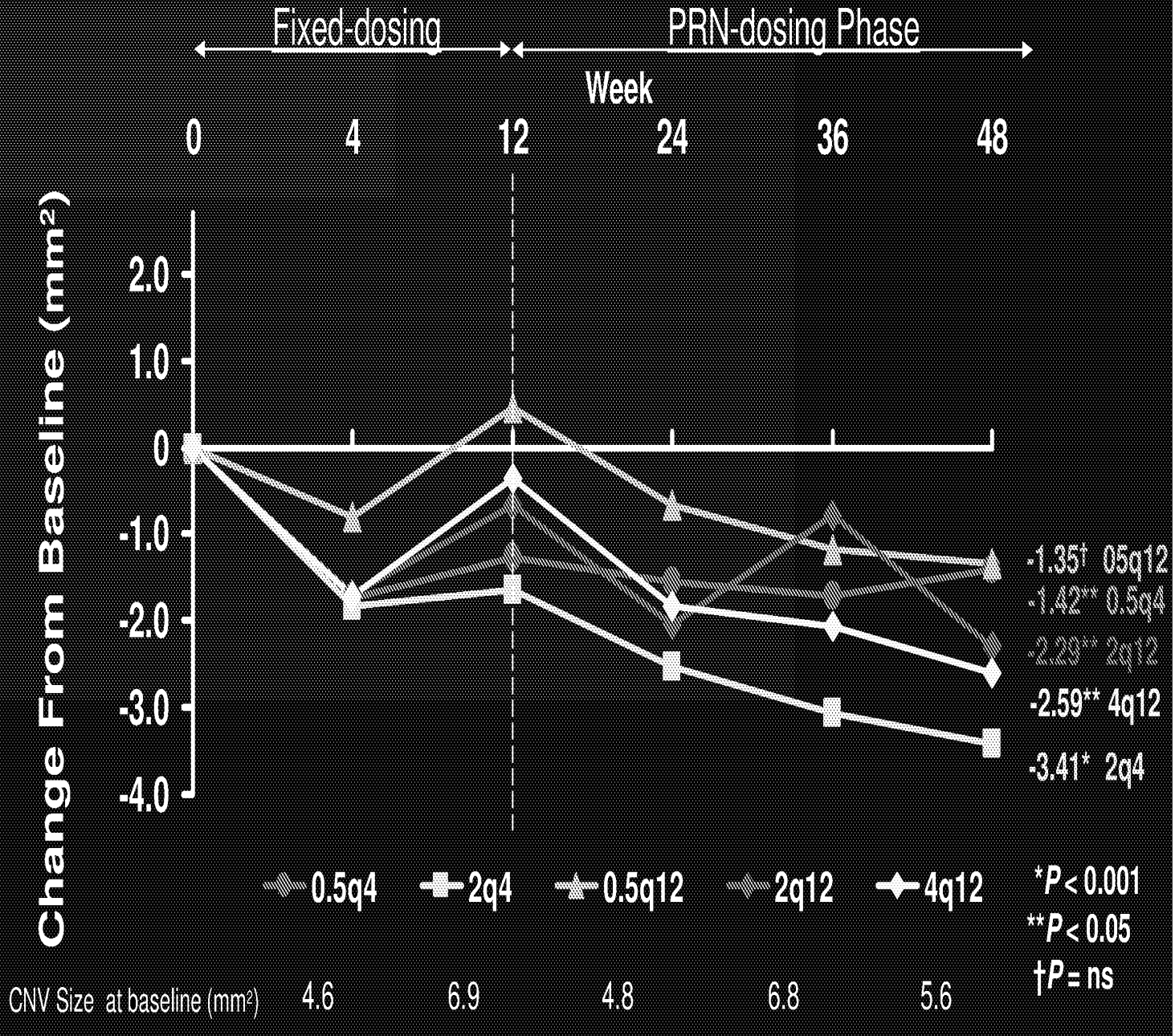
- Total Lesion Size
  - Measurement of entire lesion including the classic and occult neovascular component as well as contiguous areas of blood and/or blocked fluorescence and/or serous pigment epithelial detachment (PED)
- Total Active CNV Size
  - Area of visible CNV (classic and/or occult) which demonstrates angiographic evidence of late leakage or pooling of dye
- Classic CNV
  - Area of bright, well-demarcated hyperfluorescence in early phase, with progressive dye leakage into overlying subsensory retinal space in late phase of angiogram (not a measurement of area of leakage, but rather extent of the classic neovascular complex)
- Occult CNV
  - Angiogram shows staining or leakage from fibrovascular PED or hyperfluorescent leakage at level of RPE that represents late leakage of undetermined source (leakage in late phase without classic CNV or fibrovascular PED to account for leakage)

Mean Change in Total Lesion Size by Fluorescein Angiography



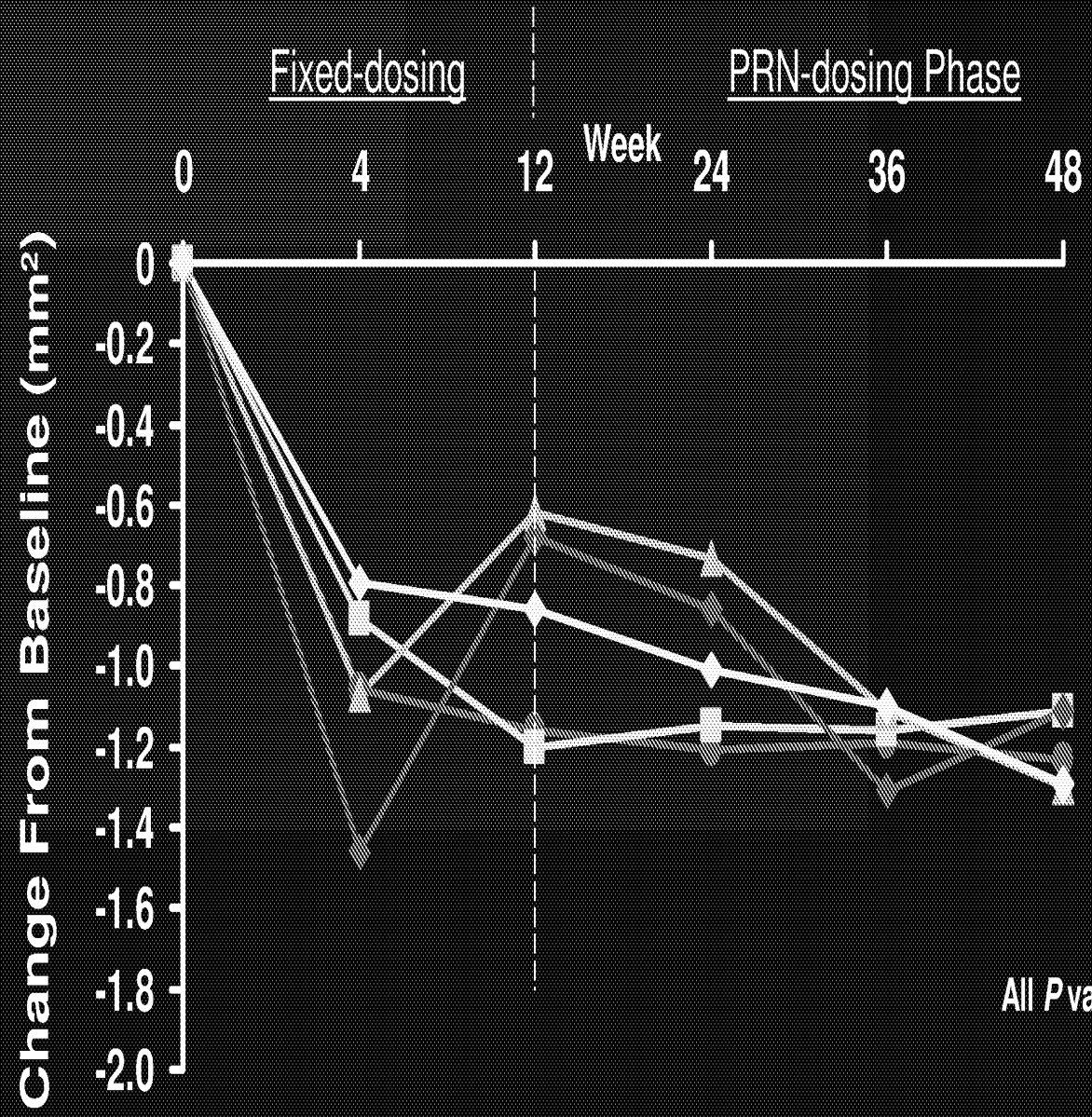
Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

Mean Change in Total Active CNV Size by Fluorescein Angiography



Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

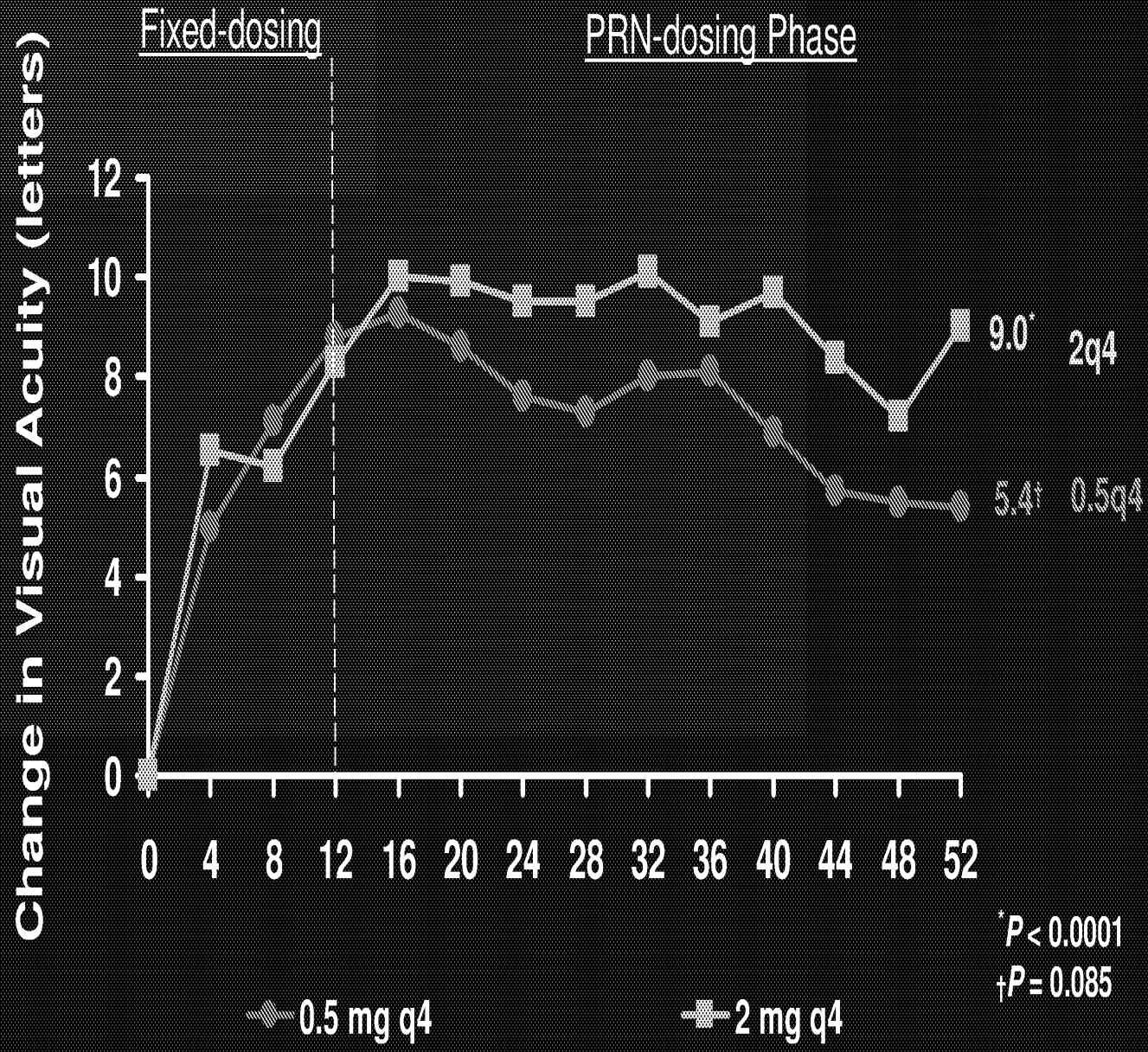
Mean Change in Classic CNV Size by Fluorescein Angiography



Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

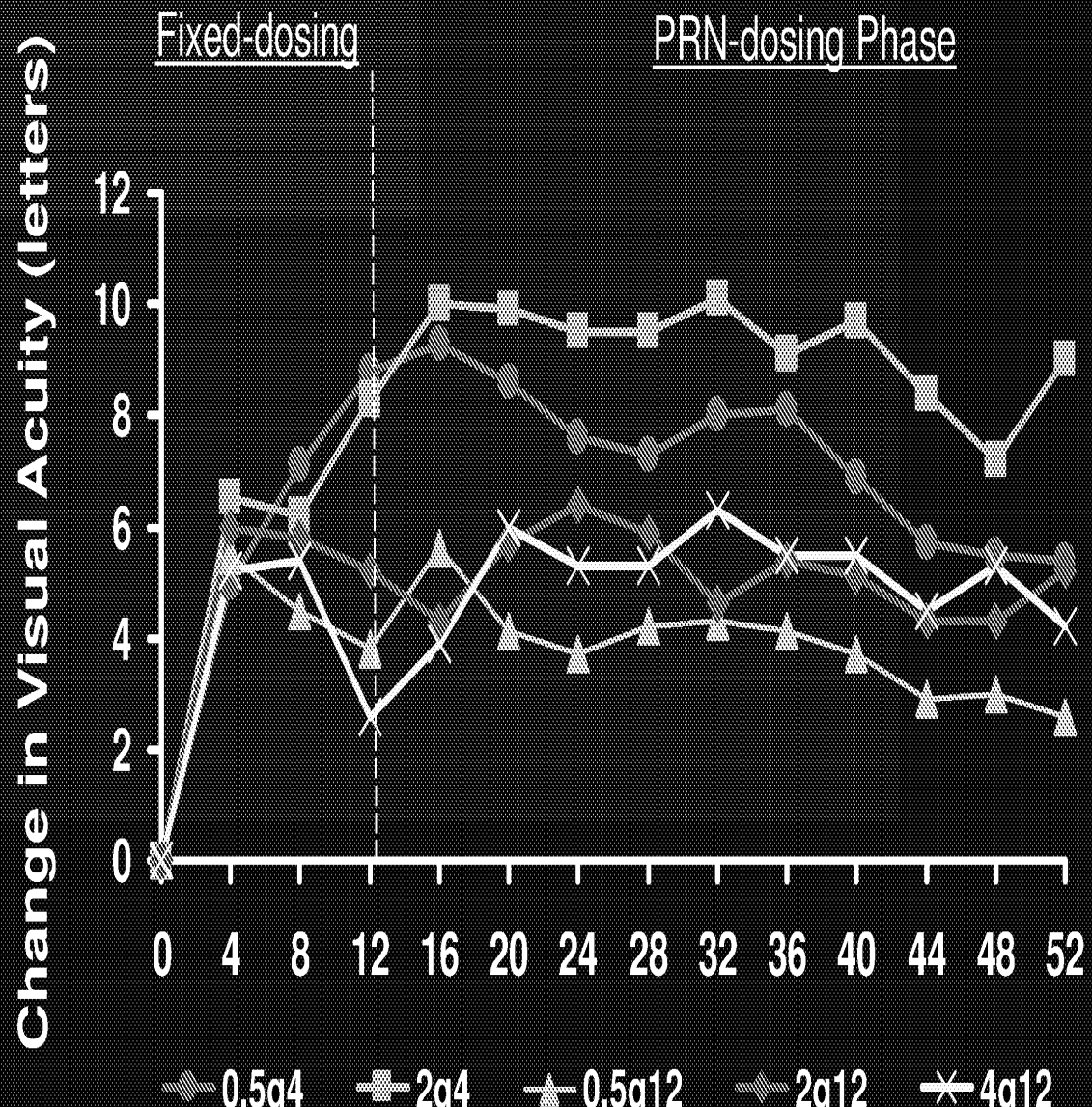
Visual Acuity

Mean Change in Visual Acuity



Last Observation Carried Forward (LOCF) analysis; paired t-test; 0.5q4 : n=32; 2q4: n=31

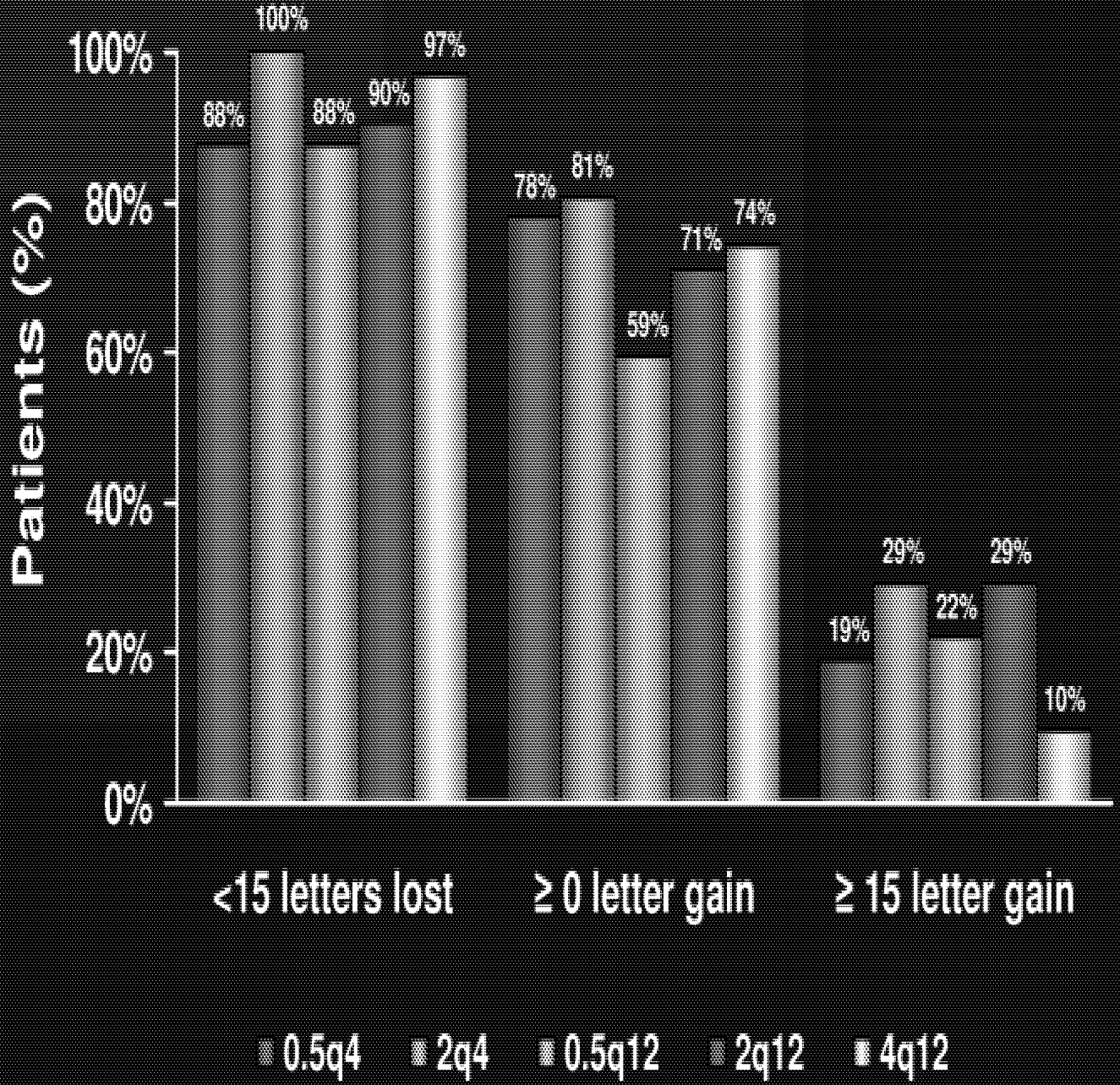
Mean Change in Visual Acuity



*$P < 0.0001$
**$P = 0.0154$
***$P = 0.0412$
†$P = 0.085$
††$P = 0.344$

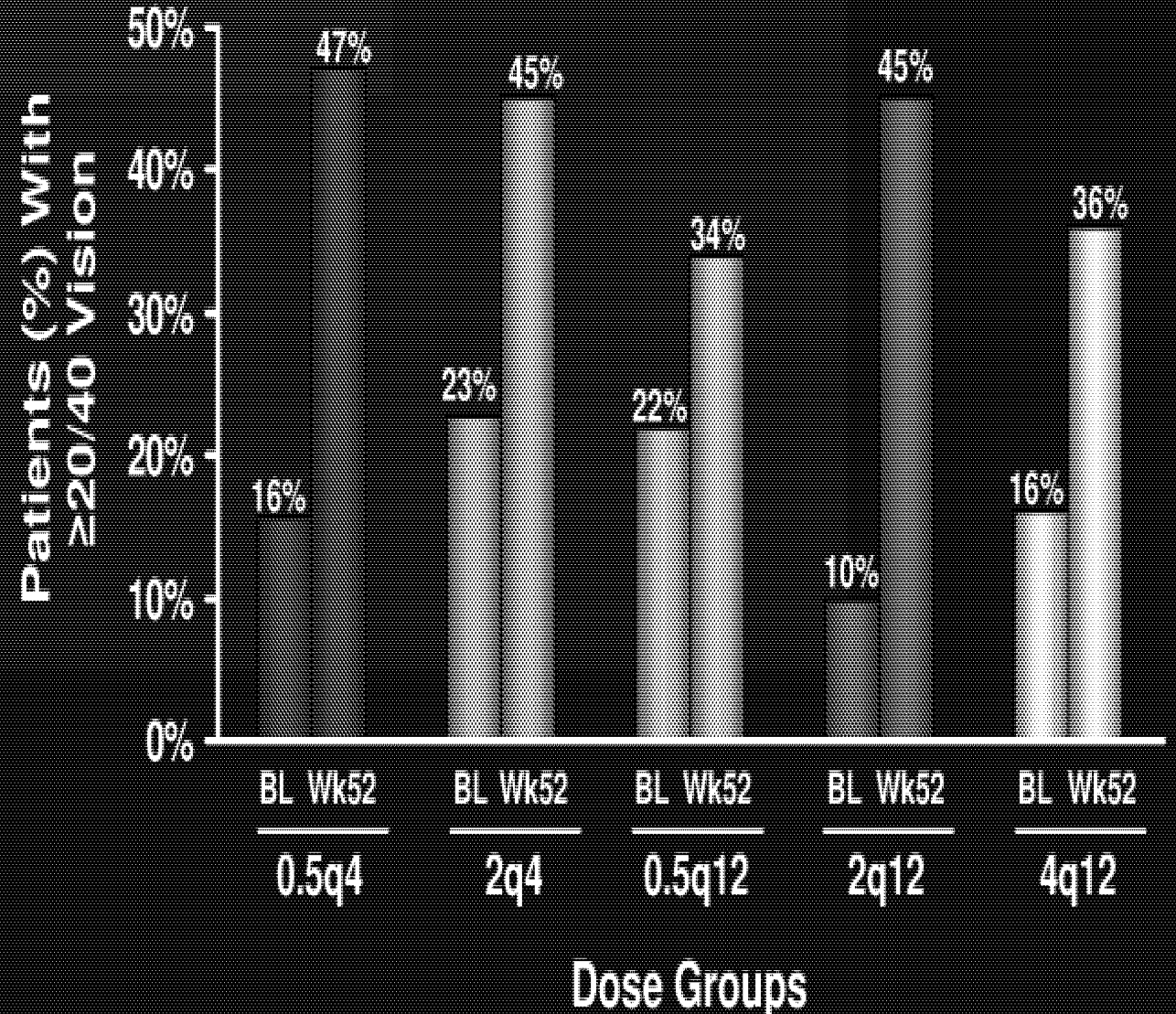
LOCF analysis; paired t-test; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

Visual Acuity at Week 52



LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

Proportion of Patients With ≥20/40 Vision



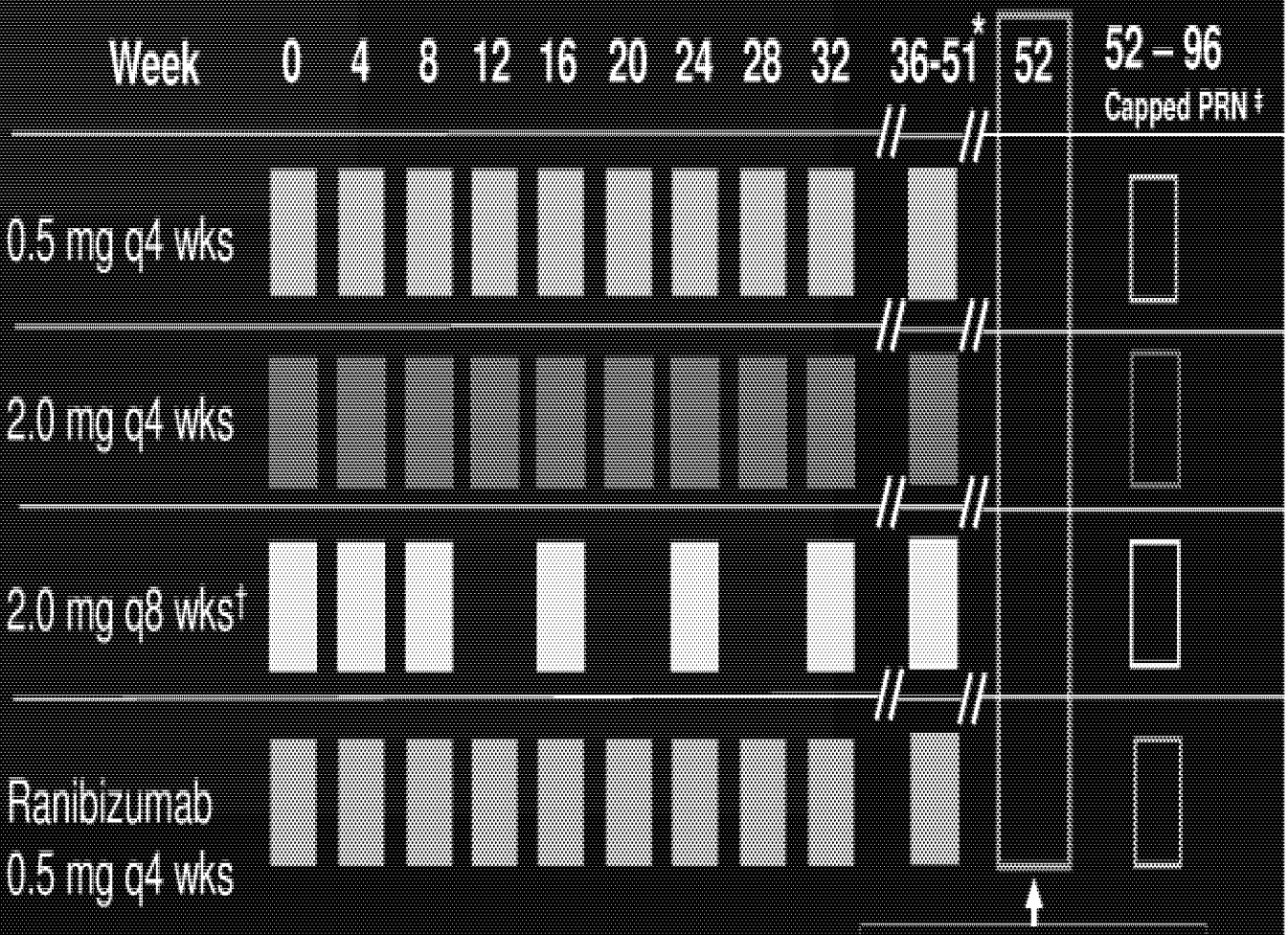
LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31; BL=baseline;

VEGF Trap-EYE
CLEAR-IT 2: 52 Week Conclusions

- Patients received, on average, only two additional injections over 40-week PRN-dosing phase (after a 12-week fixed dosing period)
  - 19% received no additional injections after Week 12
  - 110 days median time to first re-injection
- VEGF Trap-Eye achieved clinically meaningful and durable vision improvement over 1 year
  - Up to +9.0 mean letters gained at week 52
  - Up to -161 microns reduction in central retinal lesion thickness at week 52 as measured by OCT
- Generally well tolerated with no drug-related serious adverse events
  - Most common AE's typical of intravitreal injection

VIEW 1 & VIEW 2 Phase 3 Studies

(Dosing schedule-years 1 and 2)



*Continued dosing at their respective intervals

†After a loading dose period of 3-months

‡ Capped PRN: minimum injection frequency is q12 weeks

0.5 mg VEGF Trap | 2 mg q4 wks VEGF Trap | 2 mg q8 wks VEGF Trap | 0.5 mg Ranibizumab

American Academy of Ophthalmology
The Eye M.D. Association

Intravitreal Aflibercept for Diabetic Macular Edema

Jean-François Korobelnik, MD,[1,2,3] Diana V. Do, MD,[4] Ursula Schmidt-Erfurth, MD,[5] David S. Boyer, MD,[6] Frank G. Holz, MD,[7] Jeffrey S. Heier, MD,[8] Edoardo Midena, MD,[9] Peter K. Kaiser, MD,[10] Hiroko Terasaki, MD,[11] Dennis M. Marcus, MD,[12] Quan D. Nguyen, MD,[4] Glenn J. Jaffe, MD,[13] Jason S. Slakter, MD,[14] Christian Simader, MD,[5] Yuhwen Soo, PhD,[15] Thomas Schmelter, PhD,[16] George D. Yancopoulos, MD, PhD,[15] Neil Stahl, PhD,[15] Robert Vitti, MD,[15] Alyson J. Berliner, MD, PhD,[15] Oliver Zeitz, MD,[16,17] Carola Metzig, MD,[16] David M. Brown, MD[18]

Purpose: A head-to-head comparison was performed between vascular endothelial growth factor blockade and laser for treatment of diabetic macular edema (DME).

Design: Two similarly designed, double-masked, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}.

Participants: We included 872 patients (eyes) with type 1 or 2 diabetes mellitus who presented with DME with central involvement.

Methods: Eyes received either intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation.

Main Outcome Measures: The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 52. Secondary efficacy endpoints at week 52 included the proportion of eyes that gained $\geq$15 letters from baseline and the mean change from baseline in central retinal thickness as determined by optical coherence tomography.

Results: Mean BCVA gains from baseline to week 52 in the IAI 2q4 and 2q8 groups versus the laser group were 12.5 and 10.7 versus 0.2 letters ($P < 0.0001$) in VISTA, and 10.5 and 10.7 versus 1.2 letters ($P < 0.0001$) in VIVID. The corresponding proportions of eyes gaining $\geq$15 letters were 41.6% and 31.1% versus 7.8% ($P < 0.0001$) in VISTA, and 32.4% and 33.3% versus 9.1% ($P < 0.0001$) in VIVID. Similarly, mean reductions in central retinal thickness were 185.9 and 183.1 versus 73.3 μm ($P < 0.0001$) in VISTA, and 195.0 and 192.4 versus 66.2 μm ($P < 0.0001$) in VIVID. Overall incidences of ocular and nonocular adverse events and serious adverse events, including the Anti-Platelet Trialists' Collaboration–defined arterial thromboembolic events and vascular deaths, were similar across treatment groups.

Conclusions: At week 52, IAI demonstrated significant superiority in functional and anatomic endpoints over laser, with similar efficacy in the 2q4 and 2q8 groups despite the extended dosing interval in the 2q8 group. In general, IAI was well-tolerated. *Ophthalmology 2014;121:2247-2254 © 2014 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

The growing prevalence of diabetes mellitus worldwide is predicted to increase the number of afflicted individuals to 430 million by 2030.[1] Chronic hyperglycemia secondary to diabetes mellitus leads to systemic microvascular pathology throughout the body.[2] The vascular beds of the retina are typically early indicators of disease progression, and the eye serves as the initial site in which vascular damage may be diagnosed early during disease progression.[3] Indeed, the most common complication of diabetes is retinopathy; microaneurysms, blood–retinal barrier dysfunction, and capillary dropout are important contributors to diabetic macular edema (DME), the leading cause of blindness in working-age adults.[1,4] Focal laser photocoagulation has been the standard of care to manage DME ever since the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated reduction in severe vision loss with laser directed to the leaking microaneurysms (and areas of capillary nonperfusion).[5] Although a reduction in moderate and severe vision loss was demonstrated with ETDRS laser intervention, <3% of treated patients gained 15 visual acuity letters.[5] Compared with the ETDRS study, a higher percentage of eyes (15%) treated with a modified ETDRS laser protocol gained $\geq$15 visual acuity letters at 1 year in the Diabetes Retinopathy Clinical Research Network (DRCR.net) trial.[6] Recently, as a result of the RISE/RIDE studies, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have progressively replaced focal laser photocoagulation as the primary treatment for center involving macular edema. Anti-VEGF treatment administered monthly demonstrated significant visual acuity gains in a large percentage of patients and reduction of severe visual acuity loss when administered along with pro re nata (PRN) laser.[7] Although the RISE/RIDE studies, among others, resulted in a shift of the treatment paradigm for DME,

http://dx.doi.org/10.1016/j.ophtha.2014.05.006
ISSN 0161-6420/14

many patients in clinical practice may find a monthly treatment schedule difficult to maintain.

Aflibercept is composed of key domains from human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1 and has approximately 100-fold greater binding affinity to VEGF-A than either bevacizumab or ranibizumab.[8] Intravitreal aflibercept injection (IAI; also known in the scientific literature as VEGF Trap-Eye or IVT-AFL) was recently demonstrated to have clinically equivalent efficacy to monthly ranibizumab in neovascular age-related macular degeneration, whether it was administered monthly or by a more convenient regimen every 2 months after 3 initial monthly doses.[9] We report here the primary outcome results of 2 parallel, phase 3 DME studies in diverse North American, European, Asian, and Australian patient populations. These studies, VISTA^{DME} and VIVID^{DME}, compared at week 52 the efficacy and safety of focal laser photocoagulation (with sham intraocular injections) with IAI either every 4 weeks or every 8 weeks, after 5 initial monthly doses. These are the first phase 3 studies directly comparing VEGF-blockade alone with laser alone in DME.

Methods

The VISTA and VIVID studies were 2 phase 3, randomized, double-masked, active-controlled, 148-week trials. The VISTA study (registered at www.clinicaltrials.gov; NCT01363440) was conducted across 54 sites in the United States and the VIVID study (registered at www.clinicaltrials.gov; NCT01331681) was conducted at 73 sites across Europe, Japan, and Australia (Appendix 1 provides a list of study investigators; available at www.aaojournal.org). Each clinical site's respective institutional review board/ethics committee approved the study. All patients provided written informed consent. Data for this report, which presents the 52-week results, were collected between May 2011 and June 2013.

Participants and Treatments

Adult patients with type 1 or 2 diabetes mellitus who presented with central DME involvement (defined as retinal thickening involving the 1 mm central (optical coherence tomography) subfield thickness [CST]) were eligible for enrollment if best-corrected visual acuity (BCVA) was between 73 and 24 letters (20/40–20/320 Snellen equivalent) in the study eye (Appendix 2; available at www.aaojournal.org). Only 1 eye per patient was enrolled in the study. Eyes were randomized in a 1:1:1 ratio to receive either 2 mg IAI every 4 weeks (2q4), 2 mg IAI every 8 weeks after 5 initial monthly doses (from baseline to week 16) with sham injections on non-treatment visits (2q8), or macular laser photocoagulation at baseline and sham injections at every visit (laser control group). For the primary outcome at week 52, treatments were given as described from baseline to week 48 (Appendix 3; available at www.aaojournal.org); however, the studies continued with the dosing regimens as described for the IAI groups through week 148. Eyes in the laser group received IAI as needed during the third year.

Study eyes in all treatment groups were assessed for laser retreatment beginning at week 12. If any ETDRS-defined, clinically significant macular edema, for which laser has been shown to be visually beneficial, was present (defined as thickening of retina or hard exudates at $\leq$500 μm of center of the macula, or $\geq$1 zone of retinal thickening 1 disc area or larger, any part of which was within 1 disc diameter of center of the macula), study eyes in the 2q4 and 2q8 groups received sham laser and those in the laser group received active laser, but not more frequently than every 12 weeks.

Study eyes in all treatment groups could also receive additional (rescue) treatment from week 24 onward if they lost, owing to worsening DME, $\geq$10 letters on 2 consecutive visits or $\geq$15 letters at any 1 visit from the best previous measurement, and BCVA was worse than baseline. When criteria for additional treatment were met, study eyes in the 2q4 and 2q8 groups received active laser (rather than sham) from week 24 onward, whereas those in the laser group received 5 doses of 2 mg IAI every 4 weeks followed by dosing every 8 weeks.

Outcome Measures

The primary efficacy endpoint was the change from baseline in BCVA in ETDRS letters at week 52. The secondary efficacy endpoints were (a) proportion of eyes that gained $\geq$10 letters from baseline, (b) proportion of eyes that gained $\geq$15 letters from baseline, (c) proportion of eyes with a $\geq$2-step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score,[10] (d) change from baseline in CST, as determined by optical coherence tomography, (e) change from baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) near activities subscale score, and (f) change from baseline in the NEI VFQ-25 distance activities subscale score. Methodologies for measuring outcomes are described in Appendix 4 (available at www.aaojournal.org).

Statistical Analyses

Efficacy was evaluated in the full analysis sets (eyes that received study treatment and had a baseline and $\geq$1 post-baseline BCVA assessment) from each individual study. If either of the IAI groups was superior to laser in the primary efficacy endpoint, comparisons between this IAI group and laser for the secondary efficacy endpoints were then performed in a hierarchical order from (a) to (f)—as described under Outcome Measures—to control for multiplicity. Both primary and secondary efficacy endpoints were evaluated at a 2-sided significance level of 2.5%. Missing values were imputed using the last observation carried forward (LOCF) method, and for eyes that received additional treatment, the last value before additional treatment was used for analyses, censoring values after additional treatment (LOCF). Prespecified sensitivity analyses were also performed to include values after additional treatment was given (aLOCF). Safety was assessed on the integrated safety set from VISTA and VIVID, including all randomized patients who received any study treatment. Statistical methods and sample size calculation are described in Appendix 5 (available at www.aaojournal.org).

Results

Patient Disposition, Baseline Characteristics, and Treatment Experience

The VISTA study randomized 466 patients and VIVID, 406 patients, each with 1 study eye (Appendix 6; available at www.aaojournal.org). Overall, demographics and baseline characteristics of patients were similar across all treatment groups in both studies (Table 1). However, VISTA included a greater proportion of Black or African-American patients and VIVID had a greater proportion of Asian patients. In addition, more eyes in VISTA had prior anti-VEGF therapy for DME compared with VIVID (42.9% vs 8.9%, respectively). Study eyes in the 2q4 and 2q8 groups received a mean of 11.8 and 8.4 injections in VISTA, and 12.2 and 8.7 injections in VIVID,

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	VISTA			VIVID		
	Laser (n = 154)	*IAI 2q4 (n = 154)*	*IAI 2q8 (n = 151)*	*Laser (n = 132)*	*IAI 2q4 (n = 136)*	*IAI 2q8 (n = 135)*
Mean age, years (SD)	61.7 (8.7)	62.0 (11.2)	63.1 (9.4)	63.9 (8.6)	62.6 (8.6)	64.2 (7.8)
Female, n (%)	69 (44.8)	67 (43.5)	73 (48.3)	54 (40.9)	53 (39.0)	47 (34.8)
Race, n (%)						
White	131 (85.1)	128 (83.1)	125 (82.8)	106 (80.3)	109 (80.1)	106 (78.5)
Black or African American	16 (10.4)	16 (10.4)	19 (12.6)	1 (0.8)	0 (0)	1 (0.7)
Asian	3 (1.9)	5 (3.2)	2 (1.3)	25 (18.9)	27 (19.9)	27 (20.0)
Other*	4 (2.6)	5 (3.2)	5 (3.3)	0 (0)	0 (0)	1 (0.7)
Mean HbA1c, % (SD)	7.6 (1.7)	7.9 (1.6)	7.9 (1.6)	7.7 (1.3)	7.8 (1.5)	7.7 (1.4)
Patients with HbA1c >8%, n (%)	45 (29.2)	57 (37.0)	57 (37.7)	42 (31.8)	55 (40.4)	44 (32.6)
Mean duration of diabetes, years (SD)	17.2 (9.5)	16.5 (9.9)	17.6 (11.5)	14.5 (9.8)	14.3 (9.2)	14.1 (8.9)
Mean BCVA, letters (SD)	59.7 (10.9)	58.9 (10.8)	59.4 (10.9)	60.8 (10.6)	60.8 (10.7)	58.8 (11.2)
Mean central retinal thickness, μm (SD)	483 (153)	485 (157)	479 (154)	540 (152)	502 (144)	518 (147)
DRSS score,† n (%)						
10	1 (0.6)	4 (2.6)	4 (2.6)	0	0	0
20	3 (1.9)	5 (3.2)	3 (2.0)	1 (0.8)	0	0
35	5 (3.2)	7 (4.5)	9 (6.0)	2 (1.5)	0	1 (0.7)
43	60 (39.0)	49 (31.8)	52 (34.4)	36 (27.3)	31 (22.8)	28 (20.7)
47	26 (16.9)	26 (16.9)	32 (21.2)	24 (18.2)	18 (13.2)	27 (20.0)
53	42 (27.3)	52 (33.8)	40 (26.5)	35 (26.5)	44 (32.4)	42 (31.1)
61	1 (0.6)	1 (0.6)	2 (1.3)	1 (0.8)	2 (1.5)	2 (1.5)
65	10 (6.5)	4 (2.6)	5 (3.3)	0 (0)	2 (1.5)	1 (0.7)
71	1 (0.6)	4 (2.6)	1 (0.7)	0	0	0
75	1 (0.6)	0	0	0	0	0
Cannot grade	4 (2.6)	2 (1.3)	3 (2.0)	33 (25)	39 (28.7)	34 (25.2)
Prior anti-VEGF treatment, n (%)	63 (40.9)	66 (42.9)	68 (45.0)	13 (9.8)	8 (5.9)	15 (11.1)
NEI VFQ-25 score, mean (SD)						
Total	68.7 (18.1)	69.5 (19.9)	70.5 (17.1)	77.5 (15.2)	77.3 (16.2)	71.2 (17.8)
Distance activities	63.7 (23.3)	65.3 (23.5)	66.8 (22.5)	77.0 (20.9)	76.7 (21.8)	67.8 (22.9)
Near activities	56.6 (23.1)	60.1 (23.9)	58.1 (22.9)	67.4 (22.2)	68.0 (22.9)	60.8 (23.5)

2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; BCVA = best-corrected visual acuity; DRSS = Diabetic Retinopathy Severity Scale; IAI = intravitreal aflibercept injection; HbA1c = hemoglobin A1c; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire —25; SD = standard deviation; VEGF = vascular endothelial growth factor.

Full analysis set.

*In VISTA included American Indian or Alaska native, Native Hawaiian or other Pacific islander, and not reported, and in VIVID included multiracial patients.

†Level 10, none; levels 14, 15, 20, 35, and 43, mild to moderate nonproliferative diabetic retinopathy; levels 47 and 53, moderately severe/severe nonproliferative diabetic retinopathy; levels 61, 65, 71, 75, 81, and 85, mild/moderate/high-risk/advanced proliferative diabetic retinopathy.

respectively (Table 2). Eyes in the laser group received an average of 2.7 and 2.1 laser treatments in VISTA and VIVID, respectively. Additional (rescue) treatment in VISTA was given to 0.7% to 2.6% of eyes in the IAI groups compared with 31.2% of eyes in the laser group, and in VIVID to 4.4% to 8.1% of eyes in the IAI groups compared with 24.1% of eyes in the laser group (Table 2).

Primary and Secondary Endpoints

In both VISTA and VIVID, eyes treated with IAI 2q4 and 2q8 had significant BCVA improvements from baseline when compared with the laser group. The mean values ± standard deviation (SD) change from baseline BCVA in the 2q4 and 2q8 groups compared with the laser group was +12.5±9.5 letters and +10.7±8.2 letters versus +0.2±12.5 letters ($P < 0.0001$) in VISTA, and +10.5±9.5 letters and +10.7±9.3 letters versus +1.2±10.6 letters ($P < 0.0001$) in VIVID, respectively (Fig 1A). The between-group differences remained significant in favor of the IAI groups when values after additional (rescue) treatments were included in the analyses (Fig 1B). In both studies, BCVA gains with both IAI regimens were similar and significantly greater than laser in the subgroups of eyes with and without prior anti-VEGF therapy (Table 3; available at www.aaojournal.org).

In both VISTA and VIVID, significantly more eyes treated with IAI gained ≥10 and ≥15 letters from baseline at week 52. The proportion of eyes that gained ≥10 letters from baseline in the 2q4 and 2q8 groups compared with the laser group was 64.9% and 58.3% versus 19.5% ($P < 0.0001$) in VISTA, and 54.4% and 53.3% versus 25.8% ($P < 0.0001$) in VIVID, respectively (Fig 1C). The corresponding percentages for eyes that gained ≥15 letters were 41.6% and 31.1% versus 7.8% ($P < 0.0001$) in VISTA, and 32.4% and 33.3% versus 9.1% ($P < 0.0001$) in VIVID, respectively (Fig 1C). The proportion of eyes that lost ≥15 letters from baseline in the 2q4 and 2q8 groups compared with the laser group was 0.6% and 0.7% versus 9.1% in VISTA, and 0.7% and 0% versus 10.6% in VIVID, respectively. The proportion of patients who did not lose any letters from baseline

Table 2. Treatment Experience from Baseline to Week 52

Number of Scheduled Treatments, Mean (SD)	VISTA			VIVID		
	Laser (n = 154)	*IAI 2q4 (n = 155)*	*IAI 2q8 (n = 152)*	*Laser (n = 133)*	*IAI 2q4 (n = 136)*	*IAI 2q8 (n = 135)*
Laser photocoagulation	2.7 (1.1)	–	–	2.1 (1.1)	–	–
Intravitreal aflibercept	–	11.8 (2.6)	8.4 (1.3)	–	12.2 (2.6)	8.7 (1.2)
Study eyes that received additional treatment,* n (%)	48 (31.2)*	4 (2.6)*	1 (0.7)*	32 (24.1)*	6 (4.4)*	11 (8.1)*

"–" = not applicable; 2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; IAI = intravitreal aflibercept injection; SD = standard deviation.
Safety analysis set.
*Additional treatment was 2 mg IAI every 4 weeks for 5 initial doses followed by dosing every 8 weeks in the laser group, and active laser for the IAI 2q4 and 2q8 groups. Eyes in the laser group that qualified for additional treatment (48 eyes in VISTA and 32 eyes in VIVID) received a mean ± SD of 4.4±1.6 and 4.2±1.8 injections of IAI, respectively. Eyes in the 2q4 and 2q8 groups (4 and 1, respectively, in VISTA; 6 and 11 in VIVID) that qualified for additional treatment received a mean ± SD of 1.0±0 and 1.0±NE (not evaluable) laser in VISTA, and 1.7±0.5 and 1.5±0.5 lasers in VIVID, respectively.

in the 2q4 and 2q8 groups compared with the laser group was 94.2% and 92.7% versus 57.1% in VISTA, and 94.1% and 91.9% versus 62.9% in VIVID, respectively.

Significantly greater proportions of eyes treated with IAI 2q4 and 2q8 compared with those treated with laser had a ≥2-step improvement in DRSS score in both VISTA (33.8% and 29.1% versus 14.3%, respectively; $P < 0.01$) and VIVID (33.3% and 27.7% versus 7.5%, respectively; $P < 0.001$; Fig 2A). The mean value ± SD improvements from baseline in CST were robust throughout the study and were significantly greater at week 52 in the 2q4 and 2q8 groups compared with the laser group in both VISTA (−185.9±150.7 μm and −183.1±153.5 μm vs −73.3±176.7 μm, respectively; $P < 0.0001$) and VIVID (−195.0±146.6 μm and −192.4±149.9 μm vs −66.2±139.0 μm, respectively; $P < 0.0001$; Fig 2B). The mean ± SD change from baseline in NEI VFQ-25 score was significantly different only for the near activities subscale in favor of IAI 2q4 compared with laser in VISTA (9.0±20.6 vs 5.4±20.4, respectively; $P = 0.0168$; Fig 3; available at www.aaojournal.org). The NEI VFQ-25 subscale scores were similar across all treatment groups in VIVID (Fig 3; available at www.aaojournal.org).

Adverse Events

The overall incidences of ocular and nonocular adverse events were similar across treatment groups (Appendix 7; available at www.aaojournal.org). There were no clinically relevant differences between the treatment groups in terms of frequency or pattern of ocular serious adverse events (Table 4). There were no reports of endophthalmitis, or events suggestive of endophthalmitis (such as hypopyon). The incidence of intraocular inflammation based on the total number of intravitreal injections in the IAI 2q4, IAI 2q8, and laser groups was 0.2% (4/1832 injections), 0.1% (1/1284 injections), and 0.5% (1/212 injections) in VISTA, and 0.2% (4/1656 injections), 0.4% (5/1168 injections), and 0.7% (1/135 injections) in VIVID, respectively. However, both laser patients developed intraocular inflammation prior to receiving IAI.

The incidence of nonocular serious adverse events was slightly higher for some events in the combined IAI group (e.g., congestive cardiac failure and anemia), and for others in the laser group (e.g., acute myocardial infarction and osteoarthritis), with no apparent general trend (Appendix 7; available at www.aaojournal.org). The overall incidences of nonocular serious adverse events and arterial thromboembolic events defined by the Anti-Platelet Trialists' Collaboration criteria were similar across treatment groups (Appendix 7, available at www.aaojournal.org; Table 4). The number of vascular deaths in the 2q4, 2q8, and laser groups was 2, 2, and 2, respectively (Appendix 7; available at www.aaojournal.org). The total number of deaths in these groups was 2, 4, and 2, respectively, with the 2 additional nonvascular deaths in the 2q8 group attributed to B-cell lymphoma and lung neoplasm (Appendix 7; available at www.aaojournal.org). The incidences and patterns of deaths were not clinically different among treatment groups.

Discussion

The VIVID and VISTA studies provide the first head-to-head comparisons of anti-VEGF blockade alone versus laser therapy alone. The results demonstrate that IAI given either every 4 or every 8 weeks (after 5 initial monthly doses) is superior to laser and results in both significant visual acuity gains and prevention of severe visual acuity loss. The primary efficacy endpoint (change from baseline in BCVA at 52 weeks) was superior in both 2q4 and 2q8 groups compared with the laser group in both studies. The percentage of eyes in the laser group that lost ≥15 letters of vision was 9.1% in VISTA and 10.6% in VIVID, replicating the 10% loss in the laser group reported by the ETDRS study.[5] In the DRCR.net trial, 8.0% of eyes treated with a modified ETDRS laser protocol lost ≥15 letters at 1 year. In marked contrast, <1% of eyes in the IAI groups (both 2q4 and 2q8) had severe visual acuity loss. An additional benefit noted in both the IAI 2q4 and 2q8 groups include significant improvement in DRSS score, implying regression of the underlying diabetic retinopathy beyond the macular area.

The VISTA/VIVID trial design differs in several respects from previous anti-VEGF DME trials.[7,11,12] First, the trial included multiethnic populations; approximately 20% of patients in VIVID were Asian compared with approximately 5.0% of patients in the RISE/RIDE trials.[7] Approximately 43% of study eyes in VISTA had been previously treated with anti-VEGF agents (with a ≥3-month washout period) demonstrating efficacy in eyes that were not totally naïve to anti-VEGF therapy. The VISTA/VIVID trials also differed from the RISE/RIDE trials in that the active anti-VEGF agent was compared with an active control group (laser),

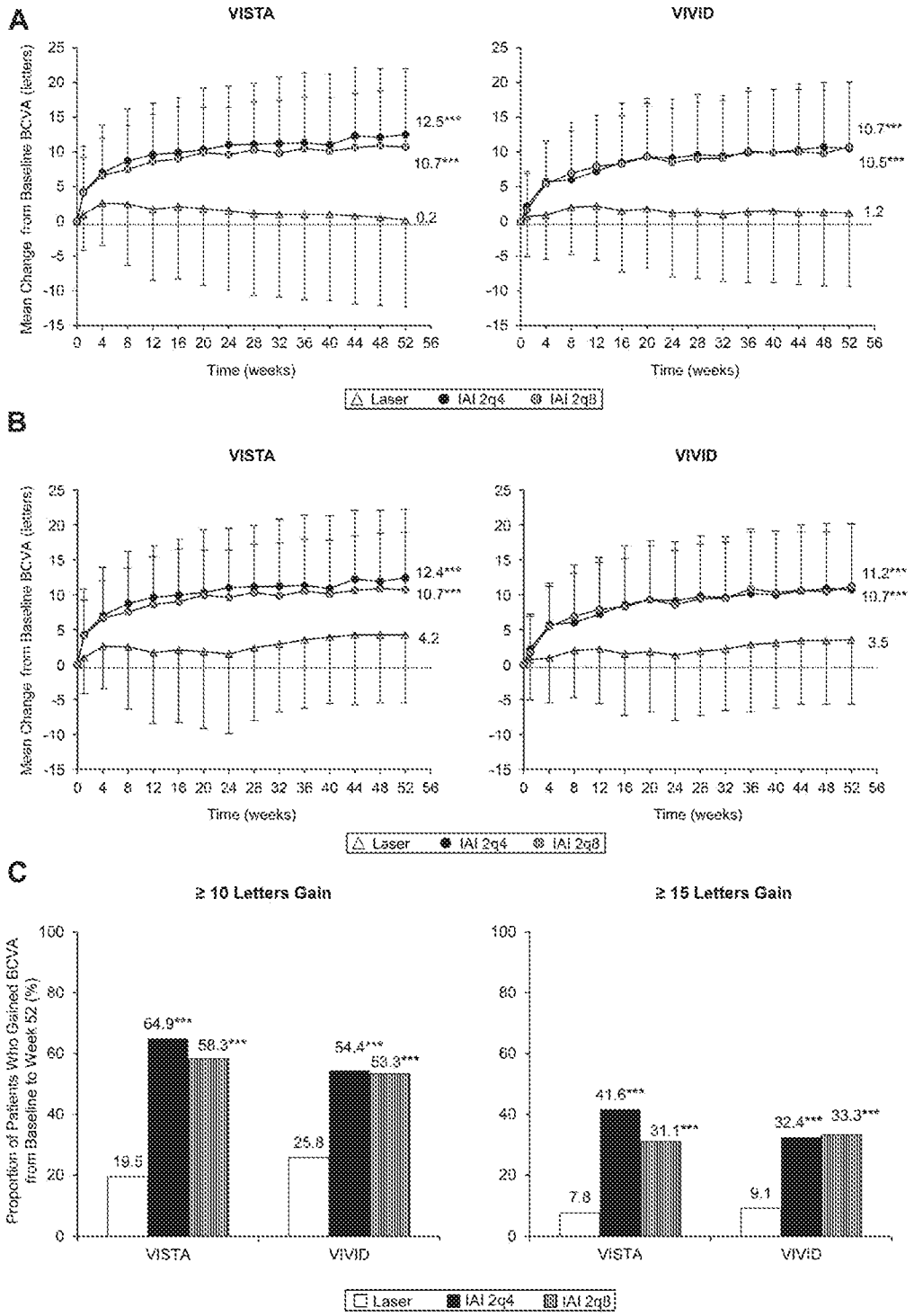


Figure 1. Visual outcomes from baseline to week 52. **A**, Mean ± standard deviation (SD) change in best-corrected visual acuity (BCVA) from baseline through week 52 with censoring of values after additional treatment was given (LOCF). **B**, Mean ± SD change in BCVA from baseline through week 52 with inclusion of values after additional treatment was given (aLOCF). **C**, Proportion of eyes that gained ≥10 and ≥15 letters from baseline to week 52 (LOCF). Full analysis set. In VISTA, n = 154 for laser, n = 154 for intravitreal aflibercept injection (IAI) 2q4, and n = 151 for IAI 2q8. In VIVID, n = 132 for laser, n = 136 for IAI 2q4, and n = 135 for IAI 2q8. ***$P < 0.0001$ versus laser from the analysis of covariance (ANCOVA) model for A and B, and Cochran-Mantel-Haenszel (CMH) test for **C**. 2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; aLOCF = last observation carried forward, including values after additional treatment was given; LOCF = last observation carried forward, censoring values after additional treatment was given; CMH = Cochran-Mantel-Haenszel; SD = standard deviation.

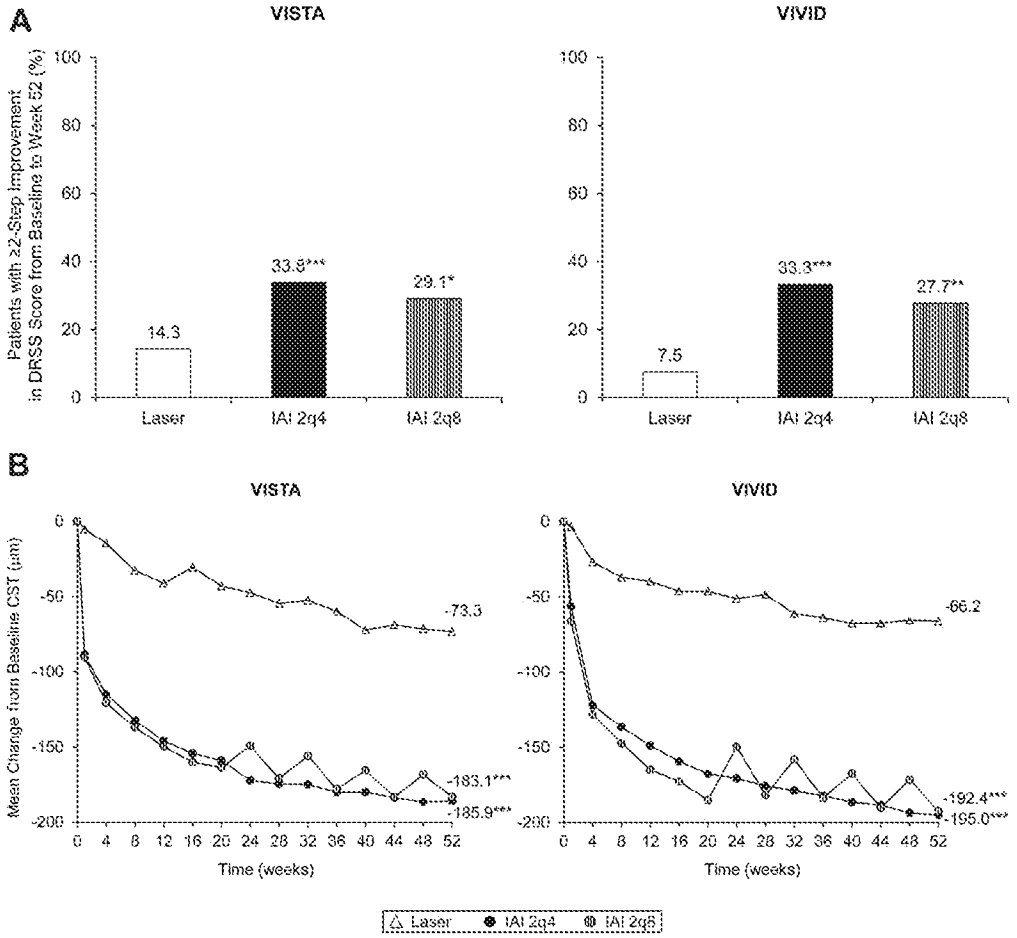


Figure 2. Additional key secondary endpoints. **A**, Proportion of eyes with a ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score from baseline to week 52. Full analysis set; last observation carried forward, censoring values after additional treatment was given (LOCF). In VISTA, n = 154 for laser, n = 154 for intravitreal aflibercept injection (IAI) 2q4, and n = 151 for IAI 2q8. In VIVID, n = 80 for laser, n = 81 for IAI 2q4, and n = 83 for IAI 2q8. **B**, Mean change from baseline in central (optical coherence tomography) subfield thickness (CST) at each study visit through week 52. Full analysis set; LOCF. In VISTA, n = 154 for laser, n = 154 for IAI 2q4, and n = 151 for IAI 2q8. In VIVID, n = 132 for laser, n = 136 for IAI 2q4, and n = 135 for IAI 2q8. *$P < 0.01$, **$P < 0.001$, and ***$P < 0.0001$ versus laser. 2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; LOCF = last observation carried forward, censoring values after additional treatment was given.

whereas the RISE/RIDE trials compared ranibizumab with sham injections. In the RISE/RIDE studies, PRN laser was available to all groups after 3 months, based on predefined anatomic criteria.[7] In contrast, the IAI groups in VIVID/VISTA could only receive laser as a rescue treatment after 24 weeks, based on significant visual acuity loss. Few eyes (<10%) in the IAI 2q4 and 2q8 groups required laser rescue and data from the time rescue laser was given was censored for the primary analysis (LOCF), thus eliminating any confounding influence from laser photocoagulation (Fig 1A). When data after additional treatment was included in the analysis (aLOCF), similar improvements were observed in the mean BCVA for these groups (Fig 1B).

Although the variability in CST in the IAI 2q8 group may suggest that anatomic suppression was not continuous with every 8-week dosing, the visual acuity results indicate that a large majority of patients with DME may be effectively treated with every 8-week dosing, given that >90% of patients in the 2q8 group did not lose any vision. Importantly, similar to the VIEW studies in patients with neovascular age-related macular degeneration,[9] there was no evidence that these optical coherence tomography fluctuations adversely translated into any corresponding limitation in visual benefit in DME patients.

Concerns about the potential systemic effects of intraocular anti-VEGF agents are particularly relevant in the diabetic population, because a large population of diabetic patients have silent ischemia in the coronary circulation.[13] In the RISE/RIDE trials, the 0.5-mg dose of ranibizumab had relatively higher rates of stroke and death compared with the 0.3-mg dose. Ranibizumab has been approved in the United States at the lower dose of 0.3 mg, and in Europe at the dose of 0.5 mg.[7] It is noteworthy that no increased rate of death, stroke, or myocardial infarction was seen in VISTA or VIVID in the IAI 2q4 group at the 52-week primary endpoint. Although differences in rates of infrequent events may not be easily detected in studies including relatively small patient populations, ongoing surveillance will continue to assess if there are any potential systemic

Table 4. Ocular Serious Adverse Events (SAEs) and APTC-Defined Arterial Thromboembolic Events from Baseline to Week 52

	Laser (n = 287)	IAI 2q4 (n = 291)	IAI 2q8 (n = 287)	All IAI (n = 578)
Ocular SAEs for study eye, n (%)	12 (4.2)	5 (1.7)	5 (1.7)	10 (1.7)
Cataract	1 (0.3)	1 (0.3)	2 (0.7)	3 (0.5)
Diabetic retinopathy	3 (1.0)	0	0	0
Macular degeneration	1 (0.3)	0	0	0
Punctate keratitis	0	1 (0.3)	0	1 (0.2)
Retinal artery occlusion	0	1 (0.3)	0	1 (0.2)
Retinal detachment	0	0	1 (0.3)	1 (0.2)
Retinal exudates	1 (0.3)	0	0	0
Retinal hemorrhage	1 (0.3)	0	0	0
Retinal neovascularization	3 (1.0)	0	0	0
Vitreous hemorrhage	4 (1.4)	2 (0.7)	1 (0.3)	3 (0.5)
Injection site injury	0	1 (0.3)	0	1 (0.2)
Increased intraocular pressure	0	0	1 (0.3)	1 (0.2)
Treatment emergent APTC events,* n (%)	8 (2.8)	9 (3.1)	10 (3.5)	19 (3.3)
Nonfatal myocardial infarction	5 (1.7)	4 (1.4)	3 (1.0)	7 (1.2)
Nonfatal stroke	2 (0.7)	3 (1.0)	5 (1.7)	8 (1.4)
Vascular death	2 (0.7)	2 (0.7)	2 (0.7)	4 (0.7)

2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; APTC = Anti-Platelet Trialists' Collaboration; IAI = intravitreal aflibercept injection; SAE = serious adverse event.
Integrated safety analysis set.
*Adjudicated by a masked committee.

effects from this therapy. Safety outcomes in these 1-year results were similar across all groups.

In summary, the 1-year results of the VISTA/VIVID studies demonstrate that IAI delivered every 4 or every 8 weeks (after 5 initial monthly doses) significantly improved visual outcomes and significantly decreased severe vision loss, while simultaneously improving the diabetic retinopathy severity score, compared with focal laser photocoagulation. Data from these ongoing studies will provide additional information regarding the similar efficacy observed with the 2q4 and 2q8 regimens of IAI. Thus, intravitreal aflibercept dosed every 8 weeks (after 5 initial monthly doses) could provide a therapeutic option that may reduce the total number of injections and necessary office visits, substantially reducing burden on patients, physicians, and the health care system.

Acknowledgments. Assistance with the study design and conduct and data analysis was provided by Karen Chu, MS, and Xiaoping Zhu, PhD, Regeneron Pharmaceuticals, Inc. (VISTA), and Jana Sachsinger, PhD, and Christiane Norenberg, MS, Bayer HealthCare (VIVID). Editorial and administrative assistance to the authors was provided by Hadi Moini, PhD, and S. Balachandra Dass, PhD, Regeneron Pharmaceuticals, Inc.

References

1. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med 2012;366:1227–39.
2. Wirostko B, Wong TY, Simo R. Vascular endothelial growth factor and diabetic complications. Prog Retin Eye Res 2008;27:608–21.
3. Stitt AW, Curtis TM. Advanced glycation and retinal pathology during diabetes. Pharmacol Rep 2005;57(suppl):156–68.
4. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: national estimates and general information on diabetes and prediabetes in the United States. 2011. Available at: www.www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed May 10, 2014.
5. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–806.
6. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064–77.
7. Nguyen QD, Brown DM, Marcus DM, et al; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789–801.
8. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis 2012;15:171–85.
9. Heier JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537–48.
10. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. Ophthalmology 1991;98(suppl):823–33.
11. Mitchell P, Bandello F, Schmidt-Erfurth U, et al; RESTORE Study Group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615–25.
12. Nguyen QD, Shah SM, Heier JS, et al; READ-2 Study Group. Primary end point (six months) results of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) study. Ophthalmology 2009;116:2175–81.
13. May O, Arildsen H, Damsgaard EM, Mickley H. Prevalence and prediction of silent ischaemia in diabetes mellitus: a population-based study. Cardiovasc Res 1997;34:241–7.

Footnotes and Financial Disclosures

Originally received: April 18, 2014.
Final revision: April 22, 2014.
Accepted: May 12, 2014.
Available online: July 7, 2014. Manuscript no. 2014-591.

[1] Service d'ophtalmologie, Hôpital Pellegrin—CHU de Bordeaux, Bordeaux, France.

[2] Université Bordeaux Segalen, Bordeaux, France.

[3] INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, Bordeaux, France.

[4] Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, Nebraska.

[5] Medical University of Vienna, Vienna, Austria.

[6] Retina-Vitreous Associates Medical Group, Beverly Hills, California.

[7] Department of Ophthalmology, University of Bonn, Bonn, Germany.

[8] Ophthalmic Consultants of Boston and Tufts University School of Medicine, Boston, Massachusetts.

[9] Department of Ophthalmology, University of Padova, Padova, Italy.

[10] Cole Eye Institute, Cleveland, Ohio.

[11] Nagoya University Hospital, Nagoya, Japan.

[12] Southeast Retina Center, Augusta, Georgia.

[13] Department of Ophthalmology, Duke University, Durham, North Carolina.

[14] Vitreous-Retina-Macula Consultants of New York, New York, New York.

[15] Regeneron Pharmaceuticals, Inc., Tarrytown, New York.

[16] Bayer HealthCare, Berlin, Germany.

[17] University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

[18] Retina Consultants of Houston, Houston, Texas.

Presented at the American Academy of Ophthalmology Annual Meeting, November 2013. This was an annual meeting paper presentation.

Financial Disclosure(s):
The authors have made the following disclosures:

Jean-François Korobelnik: Advisory Board — Allergan, Alcon, Novartis; Consultant — Carl Zeiss Meditec, Roche, Thea; Fees (review activities) — Bayer HealthCare.

Diana V. Do: Research Funding — Genentech, Regeneron Pharmaceutical, Inc.

Ursula Schmidt-Erfurth — Consultant — Alcon, Bayer HealthCare, Boehringer, Novartis; Research Funding — Allergan, Alcon, Bayer HealthCare, Novartis; Travel Support — Bayer HealthCare.

David S. Boyer: Advisory Board Member — Alcon, Allergan, Neurotech; Consultant — Alcon, Allergo, Allergan, Bausch & Lomb, Bayer, KalVista, Neurotech, Novartis, Roche, ThromboGenics, GSK; Received Research funding — Genentech, Regeneron Pharmaceuticals, Inc.; Lecture Fee — Allergan.

Frank G. Holz: Consultant — Acucela, Alcon, Allergan, Bayer HealthCare, Boehringer-Ingelheim, Genentech, Heidelberg Engineering, Merz, Novartis, Pfizer; Research Funding —Alcon, Allergan, Bayer HealthCare, Carl Zeiss Meditec, GSK, Heidelberg Engineering, Novartis, Optos; Travel Support — Bayer HealthCare; Lecture Fees — Alcon, Bayer HealthCare, Heidelberg Engineering, Novartis, Pfizer.

Jeffrey S. Heier: Consultant — Acucela, Aerpio, Alcon, Allegro, Allergan, Bayer, Forsight Vision, Genentech, Genzyme, Kala Pharmaceutical, Liquidia, Merz, Neurotech, Ohr Pharmaceutical, Oraya, Regeneron Pharmaceuticals, Inc., Sanofi, Stealth Peptides, Thrombogenics, Xcovery; Research Funding — Acucela, Aerpio, Alcon, Alimera, Genentech, Genzyme, Kato Pharmaceutical, Lpath, Novartis, Ohr, Ophthotech, QLT, Regeneron Pharmaceuticals, Inc.

Edoardo Midena: Research Funding — Bayer HealthCare.

Peter K. Kaiser: Consultant to Bayer HealthCare, Chengdu Kanghong, Genentech, Novartis, Regeneron Pharmaceuticals, Inc.

Hiroko Terasaki: Research Funding — Alcon, Novartis, Pfizer, Santen, Senju, Wacamoto; Lecture Fees — Alcon, Bayer HealthCare, Novartis, Pfizer, Santen, Senju, Wacamoto.

Dennis M. Marcus: Consultant — Genentech, Thrombogenics, Regeneron Pharmaceuticals, Inc.; Research Funding — Regeneron Pharmaceuticals, Inc., Genentech, Thrombogenics, Alcon, Allergan, Ophthotech, GSK, Pfizer, Acucela, LPath, Quark.

Quan D. Nguyen: Research Funding — AbbVie, Genentech, Optos, Regeneron Pharmaceuticals, Inc., Santen, Inc.

Glenn J. Jaffe: Consultant — Heidelberg Engineering, Neurotech; Travel Support — Regeneron Pharmaceuticals, Inc.

Jason S. Slakter: Research Funding — Acucela, Alimera, Bayer HealthCare, Fovea, Genentech, Genzyme, GSK, Kanghong Biotech, LPath, Ohr Pharma, Oraya, Regeneron Pharmaceuticals, Inc., Sanofi, XcoveryVision; Equity Owner — SKS Ocular.

Christian Simader: Payments for masked data evaluation (institutional support, Vienna Reading Center) — Bayer HealthCare, Böhringer Ingelheim, Novartis.

Yuhwen Soo: Employee — Regeneron.

George D. Yancopoulos: Employee — Regeneron; Several patents issued and pending.

Neil Stahl: Employee — Regeneron; Several patents issued and pending.

Robert Vitti: Employee — Regeneron.

Alyson J. Berliner: Employee — Regeneron.

Thomas Schmelter: Employee — Bayer HealthCare.

Oliver Zeitz: Employee — Bayer HealthCare.

Carola Metzig: Employee — Bayer HealthCare.

David M. Brown: Consultant — Allergan, Bayer HealthCare, Genentech, Genzyme, Heidelberg Engineering, Notal Vision, Novartis, QLT, Regeneron, Thrombogenics; Research Funding — Abbott, Acucela, Alimera, Allergan, Ampio, Genentech, Genzyme, GSK, Novartis, Opthotech, Pfizer, pSivida, QLT, Quark, Regeneron Pharmaceuticals, Inc., Santen, Thrombogenics, Xoma; Travel Support — Regeneron Pharmaceuticals, Inc.

The VISTA and VIVID studies were funded by Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Bayer HealthCare, Berlin, Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript.

The investigators from the VISTA and VIVID studies are listed in Appendix 1 (available at www.aaojournal.org).

Abbreviations and Acronyms:
aLOCF = last observation carried forward, including values after additional treatment was given; **BCVA** = best-corrected visual acuity; **CST** = central (optical coherence tomography) subfield thickness; **DME** = diabetic macular edema; **DRCR.net** = Diabetes Retinopathy Clinical Research Network; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IAI** = intravitreal aflibercept injection; **LOCF** = last observation carried forward, censoring values after additional treatment was given; **NEI VFQ-25** = National Eye Institute Visual Function Questionnaire-25; **PRN** = pro re nata; **VEGF** = vascular endothelial growth factor.

Correspondence:
David M. Brown, MD, Retina Consultants of Houston, 6560 Fannin Street, Suite 750, Houston, TX 77030. E-mail: dmbmd@houstonretina.com.

A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-related Macular Degeneration: Year 2 of the PrONTO Study

GEETA A. LALWANI, PHILIP J. ROSENFELD, ANNE E. FUNG, SANDER R. DUBOVY, STEPHEN MICHELS, WILLIAM FEUER, JANET L. DAVIS, HARRY W. FLYNN, JR, AND MARIA ESQUIABRO

• PURPOSE: To assess the long-term efficacy of a variable-dosing regimen with ranibizumab in the Prospective Optical Coherence Tomography (OCT) Imaging of Patients with Neovascular Age-Related Macular Degeneration (AMD) Treated with intraOcular Ranibizumab (PrONTO) Study, patients were followed for 2 years.

• DESIGN: A 2-year prospective, uncontrolled, variable-dosing regimen with intravitreal ranibizumab based on OCT.

• METHODS: In this open-label, prospective, single-center, uncontrolled clinical study, AMD patients with neovascularization involving the central fovea and a central retinal thickness (CRT) of at least 300 μm as measured by OCT were enrolled to receive 3 consecutive monthly intravitreal injections of ranibizumab (0.5 mg) [Lucentis; Genentech Inc, South San Francisco, California, USA]. During the first year, retreatment with ranibizumab was performed at each monthly visit if any criterion was fulfilled such as an increase in OCT-CRT of at least 100 μm or a loss of 5 letters or more. During the second year, the retreatment criteria were amended to include retreatment if any qualitative increase in the amount of fluid was detected using OCT.

• RESULTS: Forty patients were enrolled and 37 completed the 2-year study. At month 24, the mean visual acuity (VA) improved by 11.1 letters ($P < .001$) and the OCT-CRT decreased by 212 μm ($P < .001$). VA improved by 15 letters or more in 43% of patients. These VA and OCT outcomes were achieved with an average of 9.9 injections over 24 months.

• CONCLUSIONS: The PrONTO Study using an OCT-guided variable-dosing regimen with intravitreal ranibizumab resulted in VA outcomes comparable with the outcomes from the phase III clinical studies, but fewer intravitreal injections were required. (Am J Ophthalmol 2009;148:43–58. © 2009 by Elsevier Inc. All rights reserved.)

INHIBITION OF VASCULAR ENDOTHELIAL GROWTH FACTOR A (VEGF-A) is an effective and safe therapy for the treatment of neovascular age-related macular degeneration (AMD).[1–6] Intravitreal injections of ranibizumab (Lucentis; Genentech Inc, South San Francisco, California, USA), a recombinant, humanized, monoclonal antibody antigen-binding fragment that inhibits all the known biologically active forms of VEGF, were shown to improve mean visual acuity (VA) in eyes with neovascular AMD during the phase III clinical studies. In these studies, monthly ranibizumab injections over the course of 2 years were administered to eyes with minimally classic, occult, and predominantly classic neovascular lesions. On average, the VA letter scores improved and the outcomes were highly statistically significant.

While the phase III trials used monthly injections, it is unclear at this time if monthly dosing is the best dosing interval. Observations made after the earlier phase I/II studies with intravitreal ranibizumab suggested a role for optical coherence tomography (OCT) in determining the appropriate dosing interval for each patient. These observations came about at the completion of the phase I/II studies when subjects were enrolled in an open-label extension study that provided continued intravitreal injections of ranibizumab performed at the discretion of the investigator (Heier JS, et al. IOVS 2005;46:ARVO E-Abstract 1393). Some subjects enrolled in the extension study immediately on completion of the phase I/II trials, whereas others were delayed in their enrollment for up to 1 year after the completion of the phase I/II trials. During this period before enrollment and throughout the extension study, OCT was used to monitor the resolution and recurrence of fluid in eyes as ranibizumab therapy was started and stopped (Rosenfeld PJ, unpublished data, 2003). Patients in the extension trial usually were treated if there was evidence of recurrent leakage from choroidal neovascularization (CNV) as detected using fluorescein angiography (FA) or if there was recurrent fluid as detected using OCT imaging. This recurrence of leakage or fluid in the macula was observed either in the presence or absence

See accompanying Editorial on page 1.
Accepted for publication Jan 27, 2009.
From the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida.

Anne Fung is currently at the Pacific Eye Associates, California Pacific Medical Center, San Francisco, California. Stephen Michels is currently at the Department of Ophthalmology, University Hospital Zürich, Zürich, Switzerland.

Inquiries to Philip J. Rosenfeld, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 NW 17th Street, Miami, FL 33136; e-mail: prosenfeld@med.miami.edu

0002-9394/09/$36.00
doi:10.1016/j.ajo.2009.01.024

TABLE 1. Major Eligibility Criteria for Enrollment into the PrONTO Study

Inclusion criteria
Age 50 years or older
Active primary or recurrent macular neovascularization secondary to AMD involving the central fovea in the study eye with evidence of disease progression
OCT central retinal thickness ≥ 300 μm
Best-corrected visual acuity, using ETDRS charts, of 20/40 to 20/400 (Snellen equivalent) in the study eye
Exclusion criteria
More than 3 prior treatments with verteporfin photodynamic therapy
Previous participation in a clinical trial (for either eye) involving antiangiogenic drugs (pegaptanib, ranibizumab, anecortave acetate, protein kinase C inhibitors)
Previous subfoveal focal laser photocoagulation in the study eye
Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within 1 month preceding day 0
Subfoveal fibrosis or atrophy in the study eye
History of vitrectomy surgery in the study eye
Aphakia or absence of the posterior capsule in the study eye
History of idiopathic or autoimmune-associated uveitis in either eye

AMD = age-related macular degeneration; ETDRS = Early Treatment Diabetic Retinopathy Study; OCT = optical coherence tomography; PrONTO = Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab.

of vision loss. It became apparent that the need for retreatment varied widely among the patients and that the need for retreatment was unpredictable. In addition, it was observed that OCT seemed to detect the earliest signs of reaccumulating fluid in the macula even before leakage could be detected reliably using FA.

These observations from the patients in the extension study served as the basis for investigating whether a variable-dosing OCT-guided regimen with ranibizumab could result in fewer injections and similar clinical outcomes when compared with the phase III regimen that used monthly injections. An investigator-sponsored, open-label, prospective clinical study was designed, known as the Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab (PrONTO) Study. The 1-year results have been published,[7] and this article represents the full 2-year results of the PrONTO Study at the Bascom Palmer Eye Institute.

METHODS

PrONTO WAS A 2-YEAR, OPEN-LABEL, PROSPECTIVE, SINGLE-center clinical study designed to investigate the efficacy, durability, and safety of a variable-dosing regimen with intravitreal ranibizumab in patients with neovascular AMD. The PrONTO Study was an investigator-sponsored trial supported by Genentech Inc and performed after review by the Food and Drug Administration (FDA). Informed consent was obtained from all patients before determination of full eligibility.

TABLE 2. Timing of the Qualitative Change Retreatment Amendment in Year 2 (n = 39) of the PrONTO Study

First Visit When Amendment Active	No. of Patients
Month 17	5
Month 18	5
Month 19	3
Month 21	4
Month 22	4
Month 23	8
Month 24	5
Withdrew from study before amendment	1
Completed study before amendment	5
Total no. in study	40

PrONTO = Prospective Optical Coherence Tomography Imaging of Patients with Neovascular Age- Related Macular Degeneration Treated with intraOcular Ranibizumab.

The major efficacy endpoints were the change from baseline in VA and OCT measurements and the number of ranibizumab injections (0.5 mg) required over 2 years. At the start of the study, only 1 eye of a patient was determined to be eligible and was assigned as the study eye. The major eligibility criteria are shown in Table 1. The major inclusion criteria were the diagnosis of neovascular AMD with a baseline protocol VA letter score of 20 to 70 letters using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 2 m (Snellen equivalent of 20/40 to 20/400)[8] and an OCT central retinal thickness (CRT) of at least 300 μm. There were no exclusion criteria for preexisting cardiovascular, cerebrovascular, or peripheral vascular conditions. Of note, all FA lesion types and lesion sizes were eligible for the study.

Specifications for the digital fundus photography equipment and OCT equipment were described in the PrONTO year 1 report.[7] Angiographic lesion classification, including the diagnosis of retinal angiomatosis proliferation (RAP), was independently assessed and was confirmed by 3 study investigators as previously described.[7] All 6 high-resolution (512 A scans per B-scan) OCT diagonal scans were used to evaluate whether fluid was present in the macula and whether retreatment was needed. For the purposes of this study, fluid in the macula was identified as intraretinal fluid (cysts) or subretinal fluid, and a fluid-free macula was defined by the absence of retinal cysts and subretinal fluid as determined by OCT. Fluid under the retinal pigment epithelium (RPE), otherwise known as a pigment epithelial detachment (PED), was recorded as an

TABLE 3. Visual Acuity of Eyes with Neovascular Age-Related Macular Degeneration Treated with a Variable-Dosing Regimen of Ranibizumab through 24 Months

Study Eyes	Baseline VA Letters (Snellen Equivalent), n = 40	Month 12 VA Letters (Snellen Equivalent), n = 40	Month 24 VA Letters (Snellen Equivalent), n = 37	Change in VA Letter Scores from Baseline to Month 24,[a] n = 37
Mean (*P* value)[b]	56.2 (20/80 + 1)	65.5 (20/50; $P < .001$)	67.0 (20/50 + 1; $P < .001$)	11.1 ($P < .001$)
Median (*P* value)[c]	57 (20/80 + 2)	68 (20/40 − 2; ($P < .001$)	68.0 (20/40 − 2; $P < .001$)	14.0 ($P < .001$)

VA = visual acuity.
[a]Change in letter scores compares the 37 patients who completed the study at month 24 with their baseline scores.
[b]Paired Student *t* test.
[c]Paired Wilcoxon signed-rank test.

TABLE 4. Central Retinal Thickness of Eyes with Neovascular Age-Related Macular Degeneration Treated with a Variable-Dosing Regimen of Ranibizumab through Month 24

Patient Study Eyes	Baseline CRT (μm), n = 40	Month 12 CRT (μm), n = 40	Month 24 CRT (μm), n = 37	Change in CRT (μm) from Baseline to Month 24,[a] n = 37
Mean (*P* value)[b]	393.9	216.1 ($P < .001$)	179.3 ($P < .001$)	−211.7
Median (*P* value)[c]	384.5	199.0 ($P < .001$)	171 ($P < 0.001$)	−209.0

CRT = central retinal thickness.
[a]Change in letter scores compares the 37 patients who completed the study at month 24 with their baseline scores.
[b]Paired Student *t* test.
[c]Paired Wilcoxon signed-rank test.

OCT finding in the macula, but was not included in any of the retreatment criteria during the first year.

Eligible patients underwent VA testing and ophthalmoscopic examination at baseline, days 14, 30, 45, and 60, and then monthly thereafter. Fundus photography and OCT imaging were performed at baseline and on days 1, 2, 4, 7, 14, and 30 after the first 2 injections, and then monthly thereafter. FA was performed at baseline, months 1, 2, and 3, and then every 3 months thereafter. All ophthalmic photographers and the single OCT technician involved in the study were previously certified to participate in FDA-approved clinical trials at the Bascom Palmer Eye Institute.

Intravitreal injections of ranibizumab were administered to all patients at baseline, month 1, and month 2. Additional reinjections were given if any of the following changes were observed by the evaluating physician during the first year of the study: 1) VA loss of at least 5 letters with OCT evidence of fluid in the macula, 2) an increase in OCT CRT of at least 100 μm, 3) new macular hemorrhage, 4) new area of classic CNV, or 5) evidence of persistent fluid on OCT 1 month after the previous injection. All criteria were based on comparisons with the previous month's examination or the last time a FA was performed. If any single criterion for reinjection was fulfilled, the intravitreal injection was performed using a standard protocol previously described.[7]

During the second year, an amendment to the study changed the retreatment criteria to include any qualitative change in the appearance of the OCT images that suggested recurrent fluid in the macula. These qualitative changes included the appearance of retinal cysts or subretinal fluid or an enlargement of a PED. Any of these qualitative changes alone was sufficient to permit retreatment. Since this amendment was approved after completion of the first year, the retreatment criteria were applied to patients at different time points in the study. Table 2 shows when the retreatment amendment was applied to the patients during the study. It is important to note that the amendment was in addition to the initial criteria, not in place of them.

At the completion of the study, an audit of drug shipments revealed that the vials in the first drug shipment received from Genentech Inc had a concentration of 6 mg/ml, equivalent to a dose of 0.3 mg in a volume of 0.05 ml. It was concluded that this lower dose, which was being used concurrently in the phase II and III clinical studies, mistakenly was shipped for use in the PrONTO Study. For this reason, the first 19 patients received some 0.3-mg doses rather than the per-protocol dose of 0.5 mg. The first 7 patients received 3 monthly 0.3-mg doses, the next 7 patients received 2 monthly 0.3-mg doses, and the next 5 patients received one 0.3-mg dose at baseline. All subse-

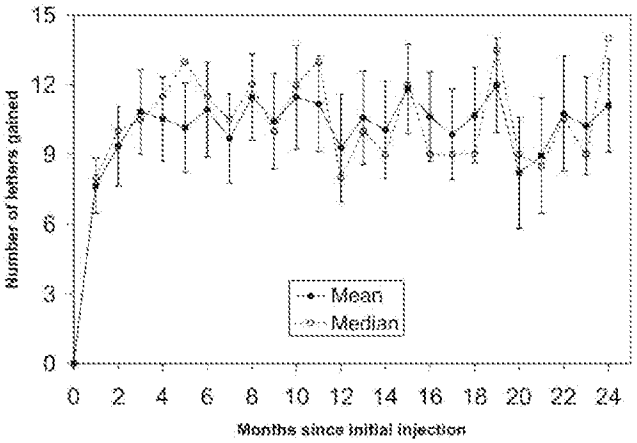


FIGURE 1. Graph showing the mean and median change in visual acuity (VA) through 24 months of eyes with neovascular age-related macular degeneration (AMD) treated with a variable-dosing intravitreal ranibizumab regimen. Vertical lines are 1 standard error (SE) of the means.

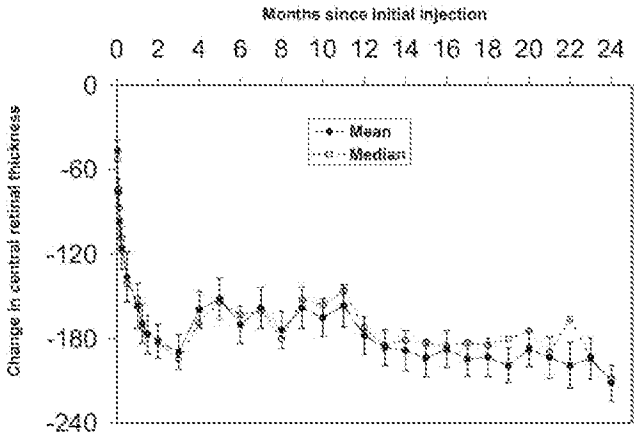


FIGURE 2. Graph showing the mean and median change in optical coherence tomography (OCT) central retinal thickness (CRT) through 24 months of eyes with neovascular AMD treated with a variable-dosing intravitreal ranibizumab regimen. Vertical lines are 1 SE of the means.

quent drug shipments and doses of drug were at the per-protocol concentration of 10 mg/ml, resulting in an intravitreal dose of 0.5 mg in 0.05 ml.

The major 2-year outcome measurements in the PrONTO Study included ETDRS VA letter scores, OCT CRT measurements, the change in VA letter scores and OCT measurements from baseline, and the total number of injections received by a patient during 2 years. For purposes of analysis, a loss of VA was defined as a drop of at least 5 letters between baseline and the 24-month time point. For the mean VA letter scores and CRT measurements, the data were compared statistically with mean baseline values using the paired Student t test. Median measurements were compared with median baseline values using the paired Wilcoxon signed-rank test. The influence of baseline FA lesion types on the number of injections over 24 months was assessed using a one-way analysis of variance and the Kruskal-Wallis test. The associations between the number of injections and VA outcomes and the associations between the change in CRT and VA outcomes at different time points during the study were assessed using the Pearson correlation analysis and Spearman nonparametric correlation analysis. Statistical significance was defined as $P < .05$.

RESULTS

• STUDY COMPLIANCE: Patient demographics and enrollment at baseline were described previously.[7] Between August 23, 2004 and April 25, 2005, a total of 69 patients were screened for the study and 40 patients were enrolled. At baseline, the mean and median VA letter scores were 56 ($20/80^{+1}$) and 57 ($20/80^{+2}$), respectively (Table 3). Baseline mean and median OCT 1-mm CRT measurements were 394 and 385 μm, respectively (Table 4). The characteristics of the neovascular lesions were described previously. Of note, the study included occult with no classic lesions (10 eyes; 25%), minimally classic lesions (23 eyes; 57.5%), and predominantly classic lesions (7 eyes; 17.5%) as characterized by FA. Overall, 10 (25%) of the 40 lesions were categorized as RAP lesions.

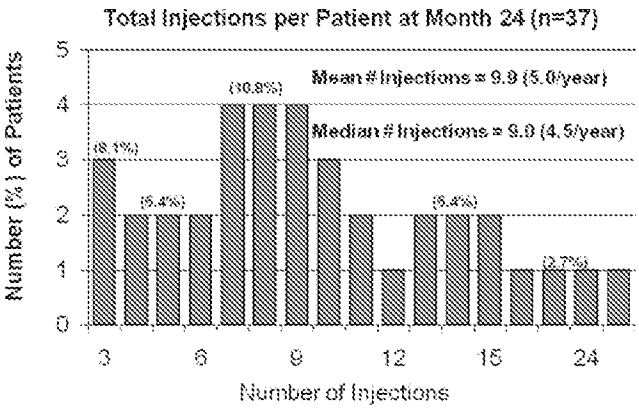


FIGURE 3. Bar graph showing the distribution of patients receiving a given number of ranibizumab injections through 24 months according to the retreatment criteria used in the Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab (PrONTO) Study.

During the second year, 3 patients withdrew from the study. One patient developed a tear of the RPE with a submacular hemorrhage and experienced a VA loss of 36 letters.[3] Submacular surgery was performed for removal of the hemorrhage and the patient withdrew from the study. The second patient was unable to travel attributable to complications after hip surgery and withdrew at month 20. The third patient died of Creutzfeldt-Jakob disease at

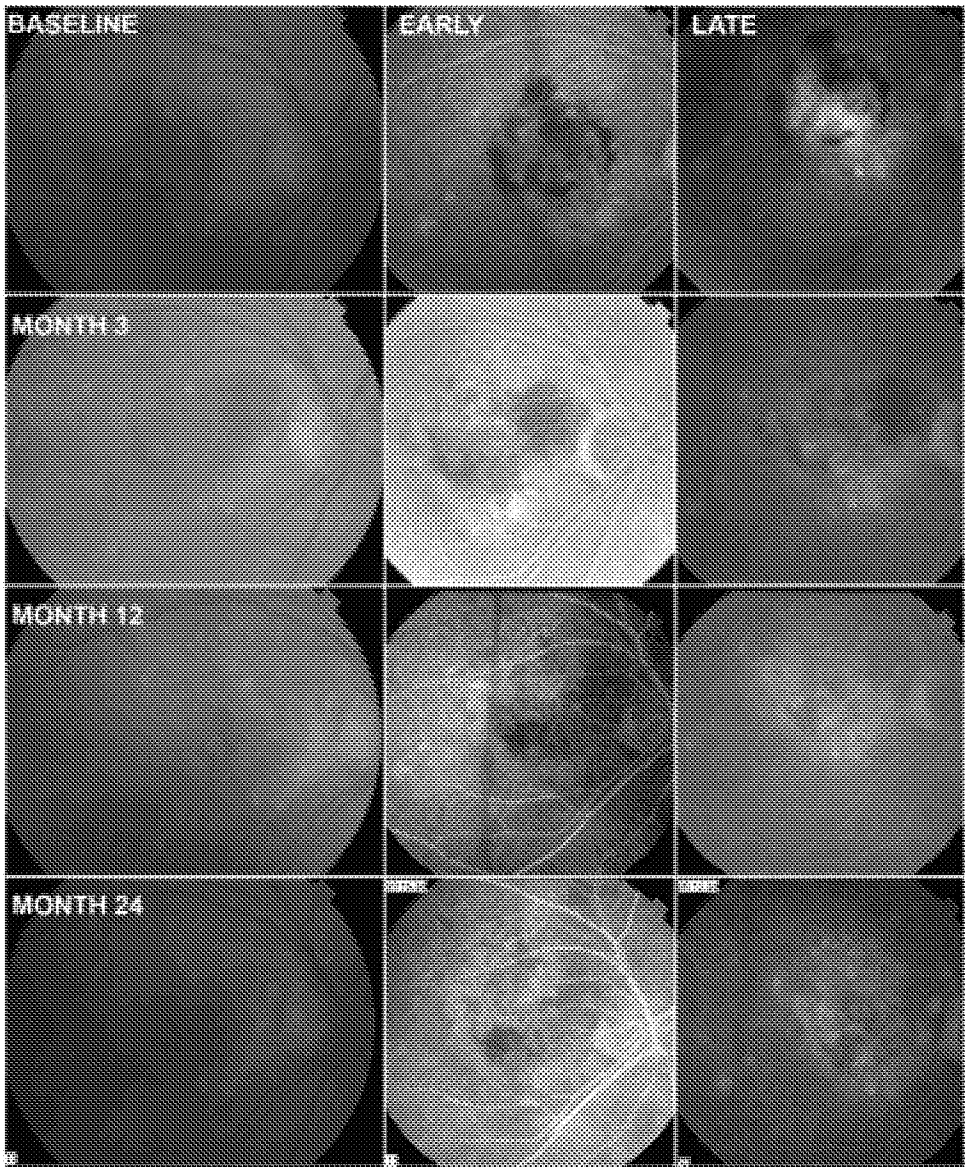


FIGURE 4. Case 1: A 74-year-old woman with neovascular AMD diagnosed with a minimally classic lesion in her right eye. She received only the first 3 required ranibizumab injections and then was followed up for 24 months. Color fundus images with early- and late-phase fluorescein angiographic (FA) images are shown at baseline, month 3 (1 month after the third injection), month 12, and month 24 without any additional injections of ranibizumab.

month 18. This death was not thought to be attributable to ranibizumab and the death was not deemed to be a drug-related adverse event. Data were analyzed from patients who completed the study (observed data set) as well from all the patients who were enrolled in the study by carrying forward their last obtained VA and OCT data before their withdrawal (last observation carried forward data set).

• VISUAL ACUITY AND OPTICAL COHERENCE TOMOGRAPHY THROUGH 24 MONTHS: The 1-year results of the PrONTO Study were reported previously.[7] Noteworthy outcomes included an improvement in VA detectable by day 14 and increases in mean and median VA scores at month 3 of 10.8 letters ($P < .001$) and 10.5 letters ($P < .001$), respectively, after the first 3 monthly injections of ranibizumab. At month 12, the improvements in mean and median VA scores compared with baseline were 9.3 letters ($P < .001$) and 11 letters ($P < .001$), respectively (Table 3; Figure 1).

At month 24, the observed final mean and median VA scores for the remaining 37 patients compared with baseline improved by 11.1 letters (standard deviation [SD], 12.2; standard error, 2.0; 95% confidence interval [CI], 7.0 to 15.2; $P < .001$) and 14 letters ($P < .001$), respectively. Sixteen eyes (43%) gained at least 3 lines of vision (95% CI, 60% to

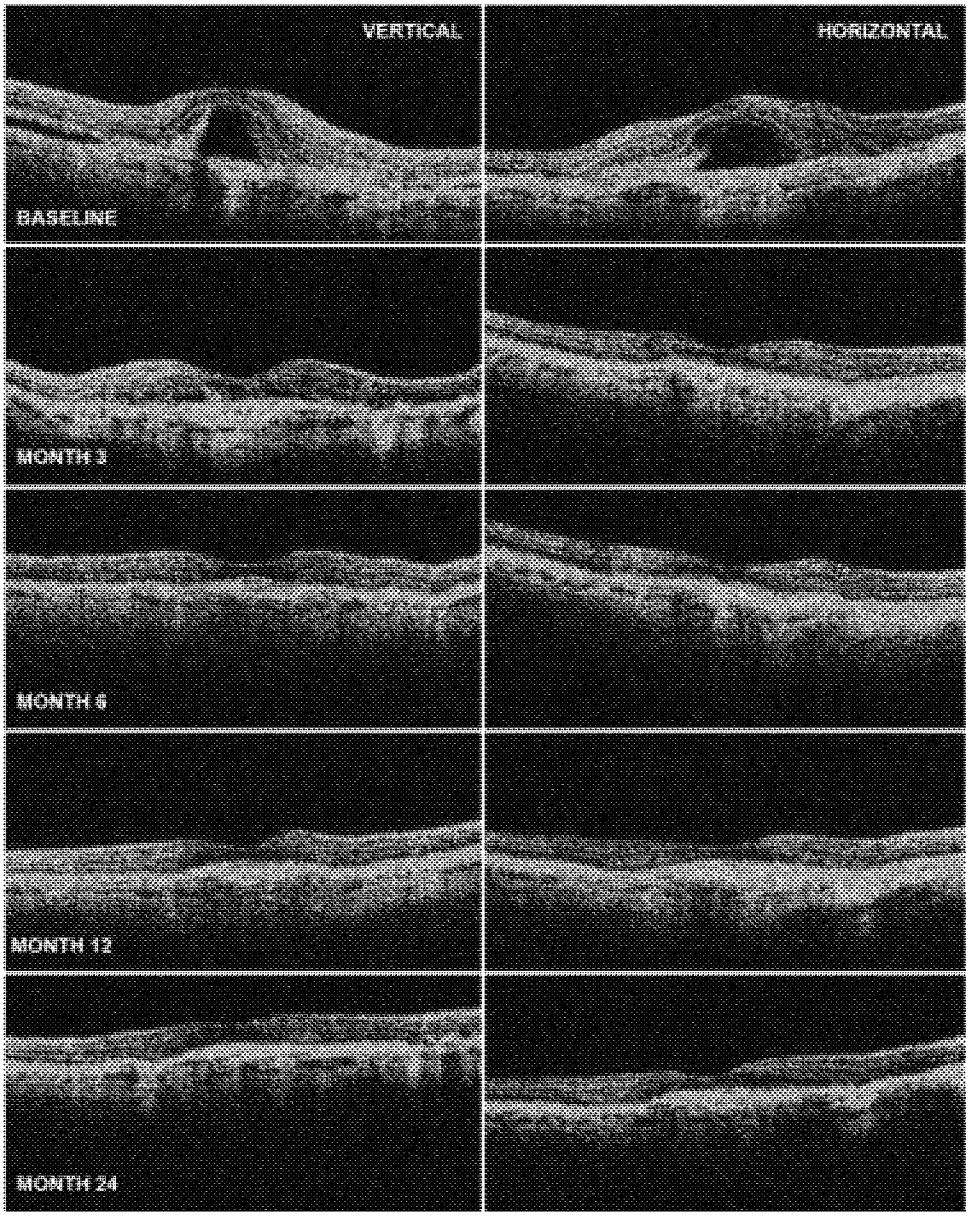


FIGURE 5. Case 1: OCT response from baseline through month 24 in an eye with neovascular AMD and a minimally classic lesion given a total of 3 injections through month 2, with no additional injections through month 24. (Left column) Vertical and (Right column) horizontal OCT scans, CRT measurements, and VA are shown of the left eye at baseline (526 μm; VA, 20/80), first ranibizumab injection; month 3 (188 μm; VA, 20/50), observed; month 6 (178 μm; VA, 20/25), observed; month 12 (198 μm; VA, 20/20), observed; month 24 (176 μm; VA, 20/16), observed.

27%), with 3 eyes (8.1%) gaining at least 6 lines of vision. Twenty-nine (78%) of the 37 eyes completing the study avoided any loss of letters (95% CI, 89% to 61%). All 37 eyes completing the study avoided a loss of 3 lines or more of VA. When calculating VA outcomes using the last observation carried forward for all 40 patients, the mean and median VA scores improved by 10.0 letters ($P < .001$) and 11.5 letters ($P < .001$), respectively, and 39 eyes (97.5%) avoided a loss of 3 lines or more.

The overall improvement in VA was associated with a decrease in CRT. At month 24, the observed mean and median thickness measurements decreased by 212 μm ($P < .001$) and 209 μm ($P < .001$), respectively (Figure 2). When the last observation was carried forward for all 40 patients, the mean and median OCT thickness measurements decreased by 222 μm ($P < .001$) and 230 μm ($P < .001$), respectively. These results were very similar regardless of whether the observed data set or the last observation carried forward data set were used in the final analyses.

These outcomes were achieved with a mean and median number of injections over 2 years of 9.9 (SD, 5.3) and 9.0

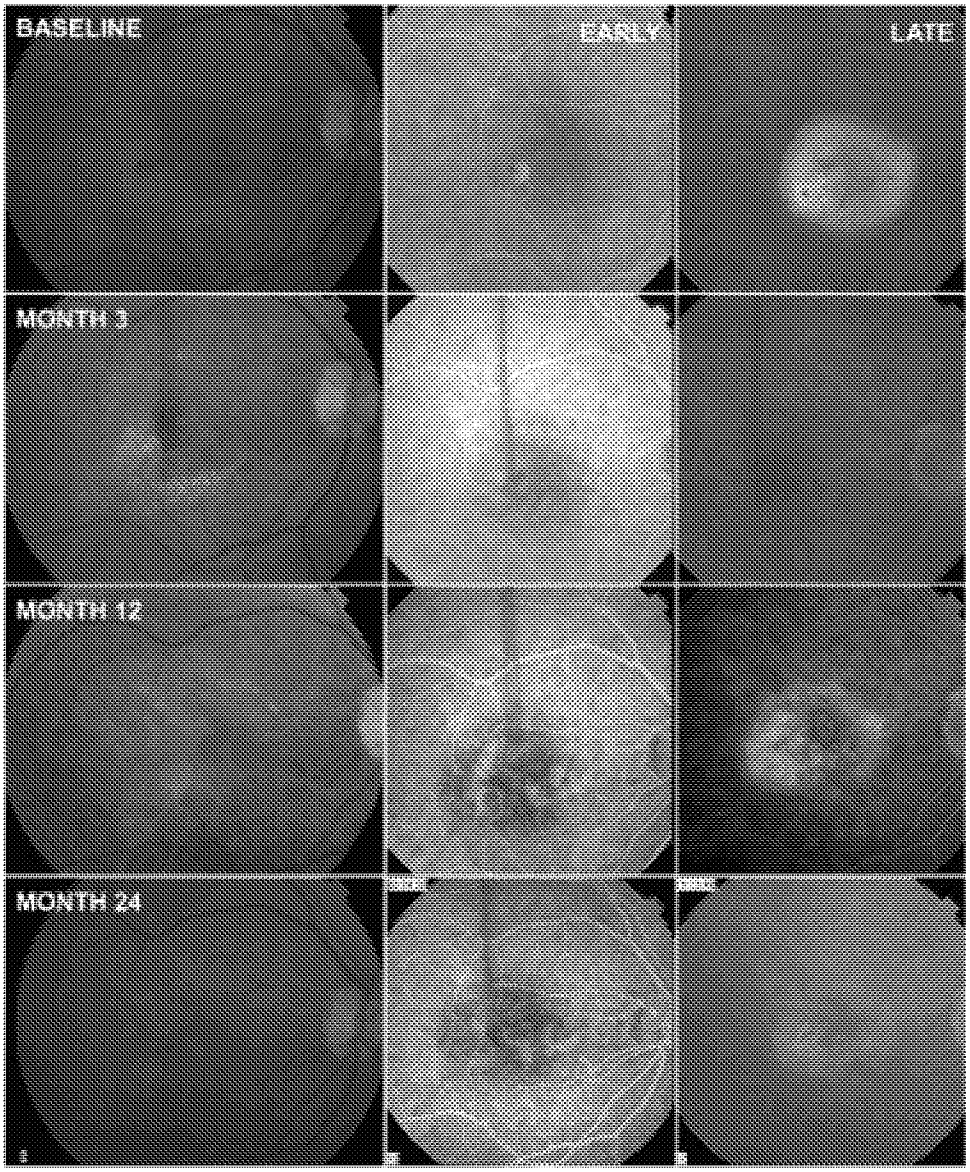


FIGURE 6. Case 2: A 68-year-old woman with AMD diagnosed with a minimally classic lesion and retinal angiomatous proliferation in her right eye. She received 24 injections over 24 months because of recurrent and persistent fluid in the macula after month 3. Color fundus images with early- and late-phase FA images are shown at baseline, month 3, month 12, and month 24. Additional ranibizumab injections were administered monthly except at month 3.

(range, 3 to 25), respectively (Figure 3). Three eyes (8.1%) required only the first 3 injections over 2 years (Figures 4 and 5), whereas 2 eyes (5.4%) required 24 or 25 injections over 2 years (Figures 6 and 7). No patient received anti–VEGF therapy in the fellow eye.

The influence of baseline VA and lesion size in disc areas on the number of reinjections was assessed with both Pearson correlation and Spearman nonparametric correlation analyses. No correlation was found between number of reinjections and baseline acuity (Pearson, r = 0.14 and P = .39; Spearman, r = −0.01 and P = .97) or lesion size (Pearson, r = 0.05 and P = .78; Spearman, r = 0.07 and P = .67). When comparing baseline angiographic lesion types with the mean number of reinjections during follow-up, we did not observe statistical significance using a one-way parametric analysis of variance (P = .67). The variation in injection rate for different lesion types was less evident during the second year of the study as compared with the first year. Overall, occult with no classic component received 10.0 injections (SD, 5.7), minimally classic lesions received 9.4 injections (SD, 4.6), and predominantly classic lesions received 11.6 injections (SD, 7.4). RAP lesions received 11.6 (SD, 5.9) injections. The tendency for RAP lesions to require more frequents retreatments during the first year was less apparent over the 2 years.

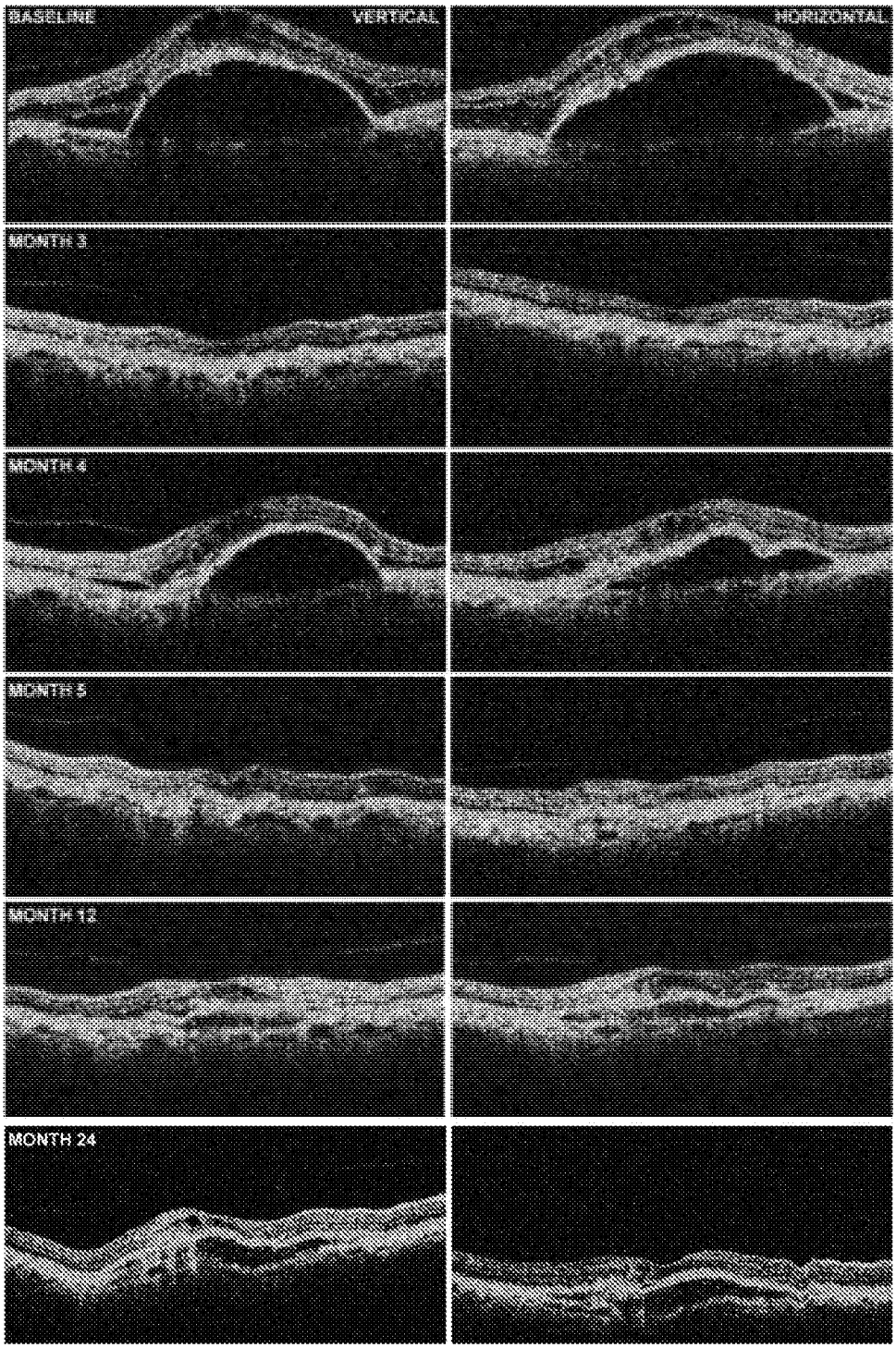


FIGURE 7. Case 2: OCT response from baseline through month 24 with a total of 24 ranibizumab injections over 24 months. (Left column) Vertical and (Right column) horizontal OCT scans, CRT measurements, and VA of her right eye are shown at baseline (345 μm; VA, 20/63), first ranibizumab injection; month 3 (164 μm; VA, 20/20), observe; month 4 (306 μm; VA, 20/40), fourth ranibizumab injection; month 5 (216 μm; VA, 20/32), fifth ranibizumab injection; month 12 (248 μm; VA, 20/25), twelfth ranibizumab injection; and month 24 (173 μm; VA, 20/25), twenty-fourth ranibizumab injection.

The influence of the number of reinjections on VA outcomes was assessed with both Pearson parametric correlation and Spearman nonparametric correlation analyses. Pearson and Spearman correlations between the change in letter scores at month 24 and the total number of injections were −0.12 (P = .48) and −0.04

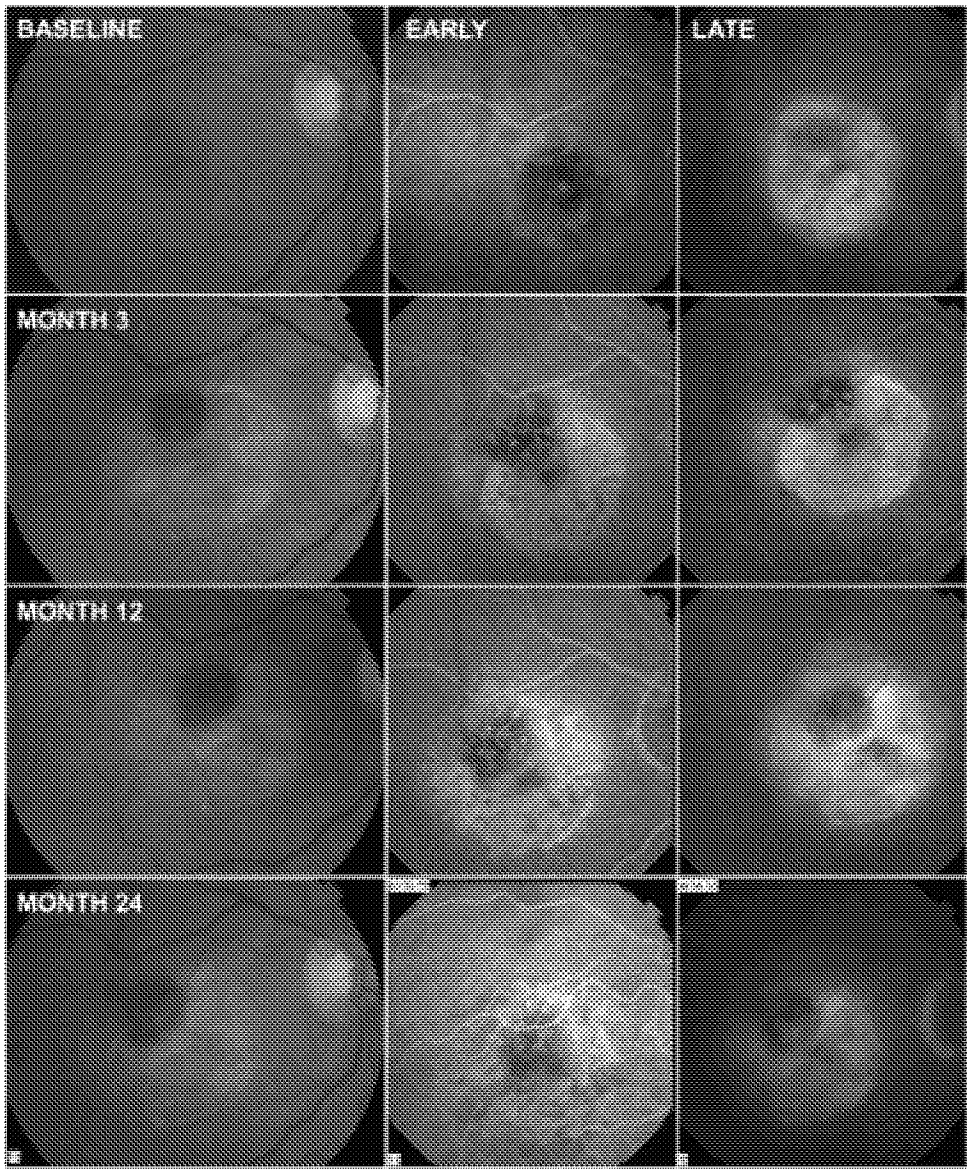


FIGURE 8. Case 3: A 96-year-old woman with neovascular AMD diagnosed with a minimally classic lesion and retinal angiomatous proliferation in the right eye. She developed a tear of the retinal pigment epithelium after the first injection. She was given seven intravitreal ranibizumab injections over 24 months. Color fundus images with early- and late-phase FA images are shown at baseline, month 3 (1 month after the third injection), month 12, and month 24. Four additional ranibizumab injections were given at month 5, month 13, month 21, and month 22.

(P = .082). No statistically significant correlation was found between the need for more frequent injections and VA outcomes.

Correlation analyses between the change in OCT-CRT and VA measurements were performed at different time points in the study to examine the predictive value of these OCT measurements. Once again, Pearson parametric and Spearman nonparametric correlations were used in these analyses. As previously reported, statistically significant correlations were found between the OCT-CRT measurements and VA at months 2, 3, and 12.[7] At month 24, no correlation was detected using either analytic technique (Pearson, r = 0.055 and P = .74; Spearman, r = 0.08 and P = .64). Another strategy was to examine the association between OCT changes at month 1 with VA changes thereafter to determine if OCT improvements could serve as a predictor of future VA improvements. Statistically significant correlations were detected when the OCT-CRT measurements at month 1 were correlated with the VA changes at month 2 (Pearson, r = 0.57 and $P < .001$; Spearman, r = 0.47 and P = .002), month 3 (Pearson, r = 0.51 and P = .001; Spearman, r = 0.36 and P = .021), month 12 (Pearson, r = 0.37 and P = .019; Spearman, r = 0.38 and P = .015), and month 24 (Pearson, r = 0.41 and P = .011; Spearman, r = 0.36 and P = .031).

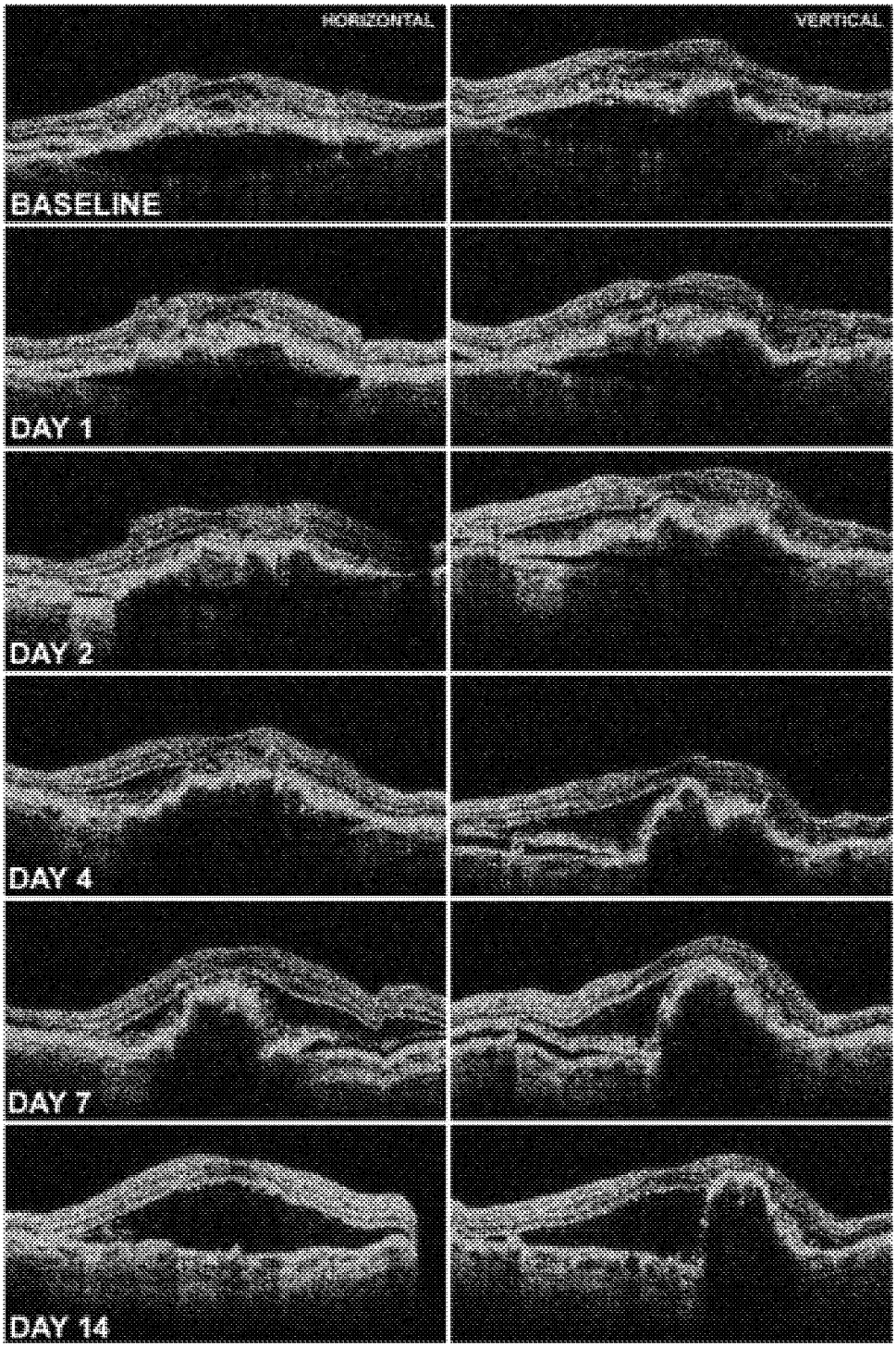


FIGURE 9. Case 3. OCT response to the first ranibizumab injection from baseline through day 14. (Left column) Vertical and (Right column) horizontal OCT scans and CRT measurements at baseline (382 μm), day 1 (400 μm), day 2 (321 μm), day 4 (295 μm), day 7 (585 μm), and day 14 (764 μm; VA, 20/25).

• VISION LOSS: For the purposes of analysis, vision loss in the PrONTO Study was defined as a loss of at least 5 letters between baseline and month 24. Of 37 eyes with complete follow-up, 29 eyes (78%) avoided any loss of letters at 24 months. Of the remaining 8 eyes, only 4 lost 5 letters or more. Of the 3 eyes that did not complete follow-up, only 1 had lost 5 letters or more at the last follow-up. Only the patient who withdrew after a submacular hemorrhage lost more than 3 lines of vision. Therefore, a total of 5 eyes lost 5 letters or more at their final follow-up visit.

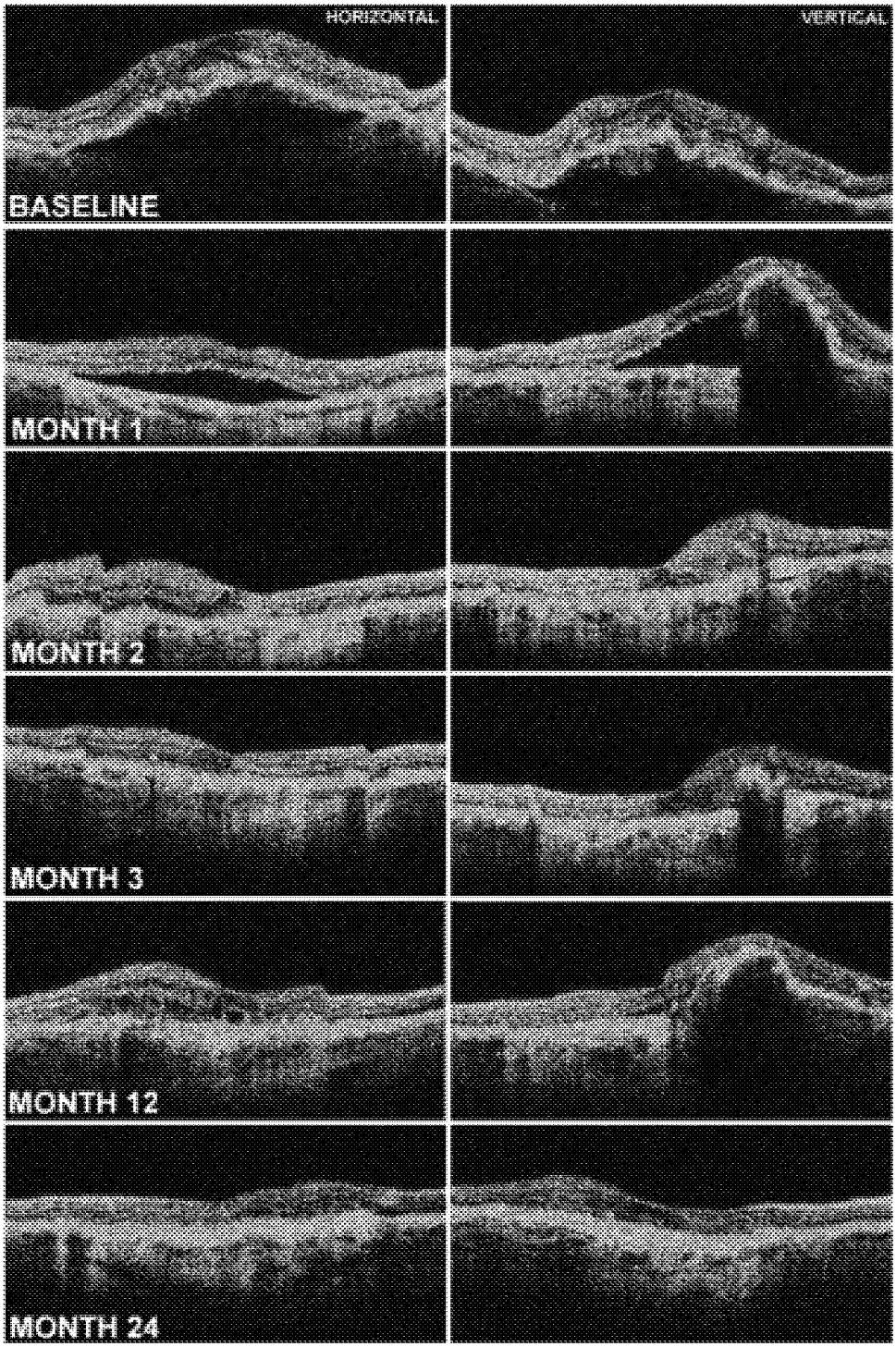


FIGURE 10. Case 3: OCT response from baseline through month 24 for a total of 7 ranibizumab injections over 24 months. (Left column) Vertical and (Right column) horizontal OCT scans, CRT measurements, and VA are shown at baseline (382 μm; VA, 20/50), month 1 (596 μm; VA, 20/200), month 2 (276 μm; VA, 20/125), month 3 (340 μm; VA, 20/160), month 12 (305 μm; VA, 20/125), and month 24 (220 μm; VA, 20/63).

Vision loss in the PrONTO Study was attributable to tears of the RPE (2 eyes; Figures 8 to 10), progression of the underlying dry AMD (2 eyes; Figures 11 and 12), and formation of subfoveal fibrosis (1 eye). Both of the eyes which developed RPE tears had minimally classic lesions characterized as RAP with an associated PED. One eye developed the RPE tear after the first injection. The evolution of the tear is depicted in Figure 9. Vision

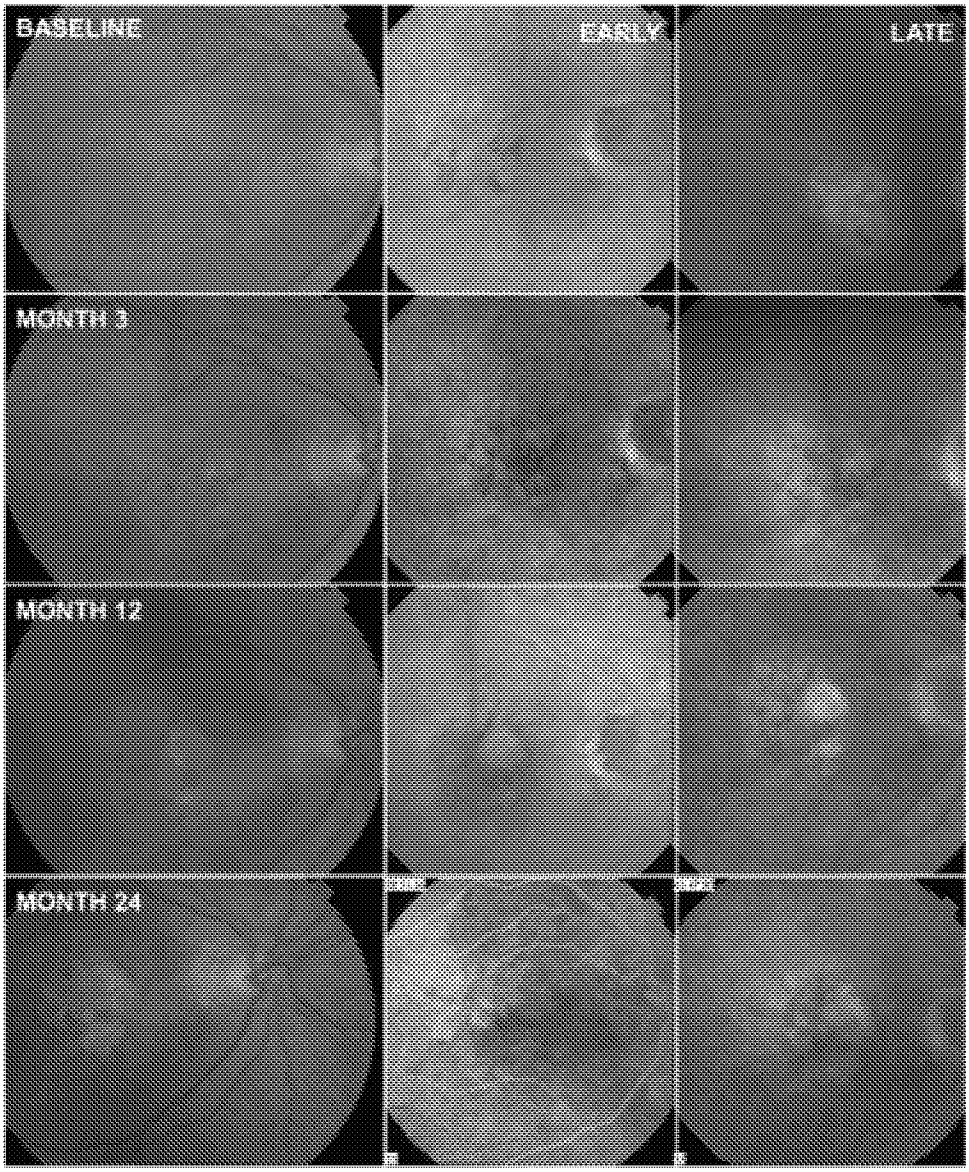


FIGURE 11. Case 4: An 89-year-old woman with AMD diagnosed with an occult-only lesion in her right eye. She achieved a fluid-free macula after the first 3 ranibizumab injections. She received a total of 9 intravitreal injections of ranibizumab over 24 months. She showed continued progression of geographic atrophy. Color fundus images with early- and late-phase FA images are shown at baseline, month 3, month 12, and month 24.

remained good until the subretinal fluid disappeared. Over the ensuing 2 years, the vision gradually improved after intermittent treatment with ranibizumab. The second eye with a tear of the RPE experienced an enlargement of the PED before the RPE tear and hemorrhage developed at the end of the first year. Prior to the hemorrhage at month 11, this patient had responded to therapy. After the initial 3 monthly injections, there was no evidence of fluid in the macula, and therefore no injection was given at month 3. Gradually, fluid reaccumulated in the macula with enlargement of a PED, but no injection was given until month 5 because none of the original quantitative retreatment criteria were fulfilled. At month 5, the patient was retreated because of a more than 100-μm increase in the OCT-CRT measurement and a loss of 11 letters. At month 6, the VA improved by 8 letters with complete resolution of the subretinal and intraretinal fluid and no injection was given. Injections were given again at month 7 and at month 9 because of reaccumulating fluid in the macula. At month 10, no fluid was detected in the retina or under the retina, so no injection was given even though the PED did show an increase in height. An increase in the height or size of a PED was not one of the retreatment criteria during the first year of the study. Shortly thereafter, before the

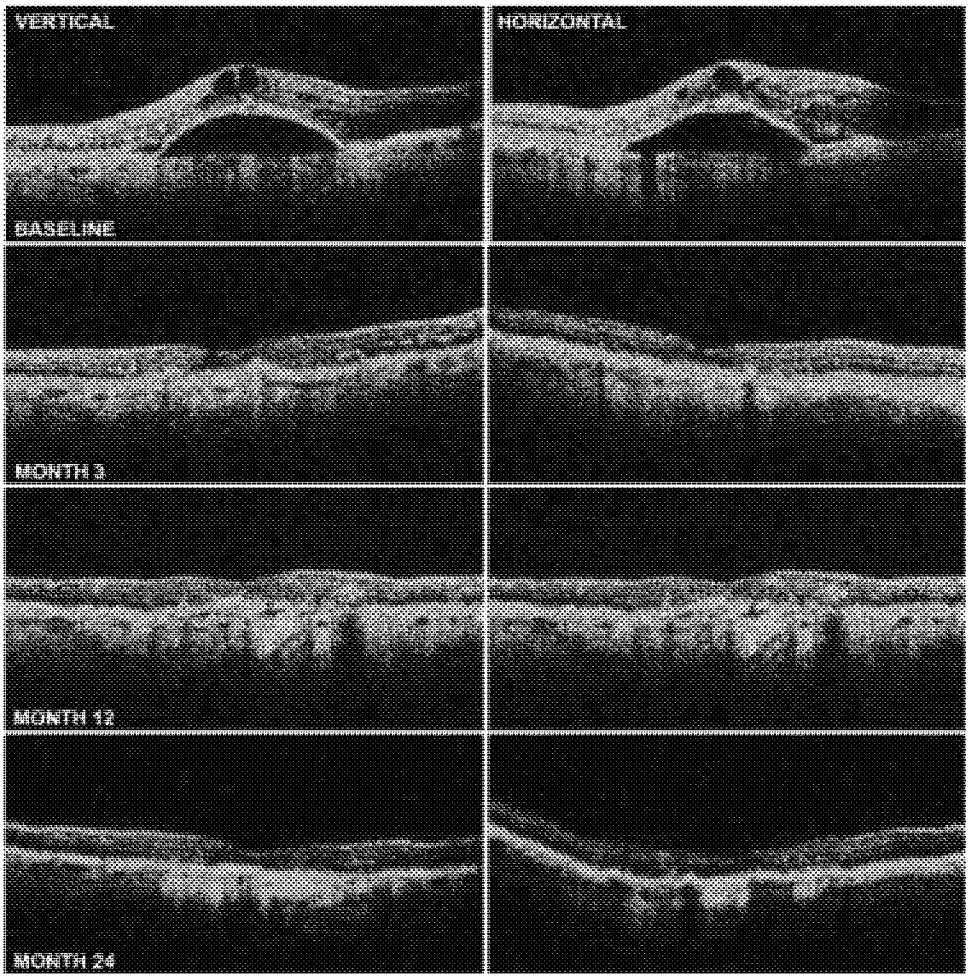


FIGURE 12. Case 4: OCT response in an eye with neovascular AMD from baseline through month 24 while receiving a total of 9 ranibizumab injections over 24 months. (Left column) Vertical and (Right column) horizontal OCT scans, CRT measurements, and VA are shown at baseline (348 μm; VA, 20/63); month 3 (187 μm; VA, 20/32), observe; month 12 (191 μm; VA, 20/40); and month 24 (160 μm; VA, 20/100).

month 11 visit, a submacular hemorrhage developed, approximately 7 weeks after the previous injection at month 9. Injections were then given at month 11 and month 12. At month 12, the VA letter score was 31 (20/250) compared with a letter score of 80 (20/25) at the month 10 visit just before the hemorrhage. The patient subsequently elected to undergo submacular surgery during month 13 and withdrew from the study. Overall, this patient received 8 injections of ranibizumab over 12 months.

Of the remaining 3 eyes with vision loss, 2 eyes had progression of geographic atrophy with gradual vision loss. These 2 eyes showed enlargement of their geographic atrophy at rates at or below 0.7 disc areas per year or 1.8 mm^2 per year. This rate was within the normal expected growth rate for geographic atrophy.[9–11] The fifth eye with vision loss had subretinal fibrosis which developed by month 3 after the 3 monthly injections and remained stable thereafter.

- **SAFETY:** There were no ocular or systemic adverse events attributable to the injection of ranibizumab. A total of 386 injections were performed without any episodes of endophthalmitis, uveitis, retinal detachment, retinal tear, vitreous hemorrhage, lens damage, cataract progression, or prolonged intraocular pressure elevation. No systemic thromboembolic events or deaths attributable to the medication occurred. No hypertension was newly diagnosed during the study.

DISCUSSION

IN THE PrONTO STUDY, INTRAVITREAL INJECTIONS OF ranibizumab were shown to improve VA and rapidly to reduce the amount of macular fluid in most patients with neovascular AMD. This decrease in retinal thickness, which was detectable within 1 day after the first injection, continued through the first 3 months and was maintained through 24 months using an OCT-guided vari-

able-dosing regimen. During the first year, strict quantitative retreatment guidelines were followed. These guidelines were developed to determine if more fluid continued to accumulate after a small amount of fluid reaccumulated in a dry macula. Another objective was to assess whether VA or OCT was better at determining when fluid was reaccumulating in the macula. It became evident that fluid continued to increase if left untreated and that the qualitative assessment of OCT B scans was better at detecting fluid in the macula than waiting for changes in VA. The need to incorporate qualitative changes into the retreatment criteria was exemplified by the 1 patient in whom a hemorrhage developed after the increase in size of the PED. Based on this and other observations, it was decided that it would be unethical to continue the strict quantitative retreatment guidelines into the second year. Therefore, the protocol was amended to permit retreatment at the earliest sign of reaccumulating fluid in the retina, under the retina, or under the RPE. The change in retreatment criteria during the second year was considered to be consistent with the study objective to determine if OCT-guided therapy could minimize the number of injections over 2 years while achieving VA outcomes comparable with the outcomes achieved using monthly injections in the phase III trials.

The final VA outcomes in the PrONTO Study were comparable with the results from the phase III clinical trials.[1,2] The PrONTO outcomes were achieved even though there was a dosing error in the first 18 patients enrolled in the study who received an initial 0.3-mg dose rather than the per-protocol 0.5-mg dose. This dosing error should not have made a difference in light of the similarity in outcomes when the 0.3- and 0.5-mg doses were compared in the phase III trials.

In the MARINA trial, the final mean VA improved by 7.2 letters, and in the ANCHOR trial, the final mean VA improved by 11.3 letters. By comparison, VA in the PrONTO Study improved by 11.1 letters at 24 months with a 95% CI ranging from 7 letters to 15.2 letters, suggesting results comparable with the phase III trial results. Whereas patients in the MARINA and ANCHOR trials received 24 injections over 24 months, the patients in the PrONTO Study received an average of just 9.9 injections with a median of 9.0 injections out of a possible 25 injections over 24 months. Other VA efficacy endpoints were comparable as well. In the MARINA and ANCHOR trials, 94.6% and 96.4% of patients avoided a 15-letter VA decrease, whereas in the PrONTO Study, 97.5% of patients avoided such a loss. In the MARINA and ANCHOR trials, 34% and 40.3% of patients gained at least 15 letters of VA compared with 43% of patients in the PrONTO Study. Finally, when comparing the proportion of patients with 0 or more letters gained at 12 months, the MARINA and ANCHOR studies reported 71.3% and 78%, whereas the PrONTO Study had 78% of patients without any letters lost. The totality of the data from the PrONTO Study suggests that OCT-guided retreatment with ranibizumab seems to be comparable with the VA outcomes from monthly injections; however, a prospective, randomized, double-masked study will be necessary to confirm these conclusions. Currently, the Comparison of AMD Treatment Trials now underway will test whether an OCT-guided variable-dosing regimen is comparable with a fixed monthly dosing regimen with intravitreal ranibizumab.

The retreatment criteria chosen for the PrONTO Study required strict monthly visits and month-to-month comparisons of all 6 OCT radial scans. These criteria were based on careful observations after the completion of the phase I/II ranibizumab studies when patients in the extension study could be treated at the discretion of the investigator. Based on that experience, it was proposed that OCT could detect the earliest signs of recurrent fluid in the macula as soon as ranibizumab therapy had dried the macula. It is important to emphasize that the criteria for retreatment depended on close follow-up with monthly visits and careful examination of all 6 diagonal OCT scans with comparisons with the previous visit's scans to determine if any fluid had persisted or reaccumulated in the macula. It was found that whenever a patient was retreated in the PrONTO Study, regardless of the criteria used, the need for retreatment could have been predicted based on careful assessment of the qualitative OCT findings alone. After publication of the first year's data, some clinicians adopted the PrONTO retreatment criteria without adopting the strict follow-up schedule, without carefully examining all 6 OCT diagonal scans, and without comparing all current scans with the scans from the previous visit. Although it may be possible to base retreatment guidelines on fewer diagonal scans and less frequent follow-up, such a regimen was not tested in the PrONTO Study, and it is not possible to extrapolate the results to other retreatment paradigms.

The PrONTO Study was designed to minimize the number of retreatments but not the number of visits. There are other strategies that may yield similar or even better VA outcomes and that require fewer visits. One such strategy is known as *treat and extend*, which is particularly appealing for use in routine clinical practice.[12] This strategy may minimize the number of clinic visits, but it may not necessarily minimize the number of reinjections. Although a PrONTO-style regimen or a treat-and-extend regimen may differ in the number of retreatments and the number of clinic visits, the overall goal is the same: to optimize VA outcomes while using OCT to maintain a dry macula in order to decrease the overall number of injections compared with monthly dosing.

The correlation between OCT retinal thickness measurements at month 1 and VA outcomes at subsequent

time points implies that the initial OCT response is a predictor of future VA improvements. The strength of the correlation is affected by the fluctuations in macular fluid that occur after the third month and the fact that OCT changes are detected before VA is affected. In addition, visual recovery after resolution of macular fluid in neovascular AMD likely depends on many variables including chronicity of disease, viability of photoreceptors and the RPE, progression of the underlying dry AMD (geographic atrophy), as well as the presence of epiretinal membranes, RPE tears, and fibrosis. Despite all these variables, the initial response to ranibizumab characterized by resolution of fluid in the macula as assessed by OCT seems to correlate with future VA improvement and may serve as a useful predictor of treatment efficacy.

In a few patients, the lack of correlation between the change in OCT retinal thickness and the change in VA can be explained by their loss of VA resulting from tears of the RPE, progression of underlying dry AMD, and the occurrence of fibrosis. These patients initially responded to therapy with a decrease in retinal thickness and a decrease in FA leakage, but proceeded to lose vision during the course of the study. This vision loss represents a true treatment failure. Moreover, the cause of this vision loss is unlike the causes of vision loss observed with previous therapies such as thermal laser, verteporfin photodynamic therapy, and pegaptanib sodium, where most of the vision loss was the result of enlarging neovascular lesions, hemorrhage, and fibrosis. For this reason, the term *ranibizumab treatment failure* should be applied to lesions associated with vision loss and not to lesions that require frequent reinjection because there was no correlation between the need for reinjection and VA outcomes.

Although ranibizumab effectively may remove the fluid from the macula and may prevent the growth and leakage of neovascular lesions, the continued progression of the underlying dry AMD explains why some patients experienced little if any VA benefit from therapy, and probably explains why some patients experience continued vision loss over an extended period while receiving ranibizumab therapy. The growth of geographic atrophy measured in the patients with vision loss was within the expected growth rate considered to be consistent with normal disease progression.[9–11] The possibility of a direct neurotoxic effect on the macula by ranibizumab seems unlikely because of absence of decreasing VA outcomes in the MARINA and ANCHOR trials over 2 years, when eyes were subjected to monthly dosing. Therefore, it stands to reason that to avoid treatment failures, therapies that target both the neovascular component and the underlying dry AMD are needed. Without this combination approach, it seems unlikely that any other antiangiogenic therapy will achieve VA outcomes better than the outcomes achieved with ranibizumab therapy alone.

In summary, the PrONTO Study used an OCT-guided variable-dosing regimen with ranibizumab resulting in VA outcomes comparable with those of the phase III studies with monthly dosing while averaging fewer than half the number of injections over 2 years.

THIS STUDY WAS SUPPORTED BY GENENTECH INC, SOUTH SAN FRANCISCO, CALIFORNIA; THE DEPARTMENT OF OPHTHALmology at the Bascom Palmer Eye Institute, Miami, Florida; an Unrestricted Grant from Research to Prevent Blindness Inc, New York, New York; Core Grant No. P30 EY014801 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland; and the German Research Foundation (DFG), Bonn, Germany. Drs Rosenfeld and Fung received research grants from Genentech Inc. Drs Rosenfeld, Fung, Davis, and Michels received clinical research grants from Novartis Ophthalmics, Alcon Laboratories, CoMentis, and Quark. Drs Rosenfeld, Fung, Michels, Davis, and Flynn have participated in competing scientific advisory boards and have received honorarium and reimbursement for travel expenses. Involved in design of study (P.J.R., A.E.F., S.M., M.E.); conduct of study (P.J.R., G.A.L., A.E.F., M.E.); data collection (P.J.R., S.D., J.D., H.W.F.); management (P.J.R., A.E.F., M.E., S.D.), analysis (P.J.R., G.A.L., W.F.), and interpretation of data (P.J.R., G.A.L., W.F.); and preparation (G.A.L., P.J.R., W.F.), review and approval of the manuscript (G.A.L., P.J.R., A.E.F., S.D., S.M., H.W.F., J.D., M.E.). Before the initiation of the study, approval to perform the PrONTO Study was obtained from the FDA and the Institutional Review Board at the University of Miami Miller School of Medicine. The study was registered with www.clinicaltrials.gov (no. NCT00344227). The study was performed in accordance with Health Insurance Portability and Accountability Act regulations.

REFERENCES

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
2. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR Study. Ophthalmology 2009;116:57–65.e5.
3. Boyer DS, Antoszyk AN, Awh CC, Bhisitkul RB, Shapiro H, Acharya NR. Subgroup analysis of the MARINA Study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114:246–252.
4. Kaiser PK, Blodi BA, Shapiro H, Acharya NR. Angiographic and optical coherence tomographic results of the MARINA Study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114:1868–1875.
5. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. Am J Ophthalmol 2007;144:850–857.
6. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–248.

7. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable-dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143:566–583.
8. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report 1. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Arch Ophthalmol 1999;117:1329–1345.
9. Sunness JS, Bressler NM, Tian Y, Alexander J, Applegate CA. Measuring geographic atrophy in advanced age-related macular degeneration. Invest Ophthalmol Vis Sci 1999;40:1761–1769.
10. Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. Ophthalmology 1999;106:1768–1779.
11. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol 2007;143:463–472.
12. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am J Ophthalmol 2007; 143:679–680.

Biosketch

Geeta A. Lalwani, MD, graduated with honors in Chemistry and East Asian Studies from Smith College in 1994 and received her MD from MCP-Hahnemann School of Medicine in 2001, where she was elected into the Alpha Omega Alpha honor society. Dr Lalwani completed her ophthalmology residency at Case Western University and a subsequent fellowship in vitreoretinal surgery at the Bascom Palmer Eye Institute in Miami, Florida. In 2007, she joined the faculty at the Bascom Palmer Eye Institute where she continues clinical research in numerous areas.

MACULAR HEMORRHAGE IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION AFTER STABILIZATION WITH ANTIANGIOGENIC THERAPY

JONATHAN P. LEVINE, MD,* INNA MARCUS, MD,†
JOHN A. SORENSON, MD,‡§ RICHARD F. SPAIDE, MD,‡§
MICHAEL J. COONEY, MD, MBA,‡§ K. BAILEY FREUND, MD‡§

Purpose: To study patients with neovascular age-related macular degeneration (AMD) who experienced a macular hemorrhage after stabilization with intravitreal antivascular endothelial growth factor (anti-VEGF) agents to improve current treatment regimens and prevent disease progression.

Methods: Retrospective chart review of six patients. The main outcome measures included time between last intravitreal anti-VEGF treatment and date of hemorrhage, time between last office visit and date of hemorrhage, and visual acuity before and after hemorrhage.

Results: Three of 6 eyes had a macular hemorrhage within 4 weeks of a stable examination. One eye had optical coherence tomography (OCT) that demonstrated no fluid 1 day before the macular hemorrhage. The average time between the date of the last injection and macular hemorrhage was 16.8 weeks (range, 7.3–28.9 weeks). The average time between the last stable examination and an event was 4.2 weeks (range, 1 day to 7.3 weeks). Three of six patients had a persistent decline in vision after the hemorrhage. Among the 4 patients, who had better than 20/200 vision before the macular hemorrhage, 2 dropped to 20/200 or worse.

Conclusion: Sight-threatening macular hemorrhages from AMD can occur within days to weeks after a stable examination and absence of fluid on OCT. Regimens that treat "as needed" based on clinical findings and OCT may not be appropriate for certain patients.

RETINA 29:1074–1079, 2009

Bevacizumab and ranibizumab have been welcomed as breakthrough antiangiogenic therapies for the treatment of neovascular AMD.[1–6] The phase IIIb studies of ranibizumab demonstrated the efficacy of monthly intravitreal injections in improving visual outcomes in eyes with neovascular AMD for up to 2 years. More recently, the PrONTO trial, a small nonrandomized study, suggested that a variable dosing regimen, using OCT as a guide for retreatment, could also achieve good visual results with the advantage of fewer treatments than a monthly dosing regimen.[7] Despite the efficacy of existing regimens, sight-threatening recurrences of macular exudation remain a concern for the treating physician. Furthermore, although OCT has become the standard of care for monitoring patients receiving anti-VEGF therapy, it remains unproven whether OCT will reliably detect evidence of recurrent neovascular activity before a visually significant macular hemorrhage.

We present a case series of six eyes with neovascular AMD stabilized after intravitreal bevacizumab or ranibizumab treatment that subsequently developed a sight-threatening macular hemorrhage.

Methods

We reviewed the records of six patients with a history of neovascular AMD at one clinical center

From the *Albert Einstein College of Medicine, Bronx, New York; †New York University School of Medicine; ‡Vitreous-Retina-Macula Consultants of New York; and §The LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Hospital, New York, New York.

Supported in part by The LuEsther T. Mertz Retinal Research Center of the Manhattan Eye, Ear, & Throat Hospital and The Macula Foundation, Inc.

Reprint requests: K. Bailey Freund, MD, Vitreous-Retina-Macula Consultants of New York, 460 Park Avenue, 5th Floor, New York, NY 10022; e-mail: vrmny@aol.com

who were initially stabilized with intravitreal bevacizumab or ranibizumab therapy and who subsequently developed a new sight-threatening macular hemorrhage between February 2006 and July 2007. All lesion types were included in this analysis, including those with significant areas of subretinal fibrosis. All patients initially received monthly injections of an anti-VEGF agent until stable. Stability was defined as complete resolution of both intraretinal and subretinal fluid detected on OCT and resolution of all macular hemorrhage when present. Persistent serous pigment epithelial detachment was not an exclusionary criterion. After stabilization, patients either received less frequent maintenance injections ("treat and extend") or were observed for signs of recurrent neovascular activity at the discretion of the treating physician.

We defined a "sight-threatening" macular hemorrhage as a subretinal hemorrhage of any size within 200 μm of the foveal center or a subretinal hemorrhage of at least 2 disk areas within the temporal vascular arcades. All eyes had not shown any signs of choroidal neovascularization activity such as macular hemorrhage or fluid on OCT on the most recent examination and OCT before the occurrence of macular hemorrhage. Information regarding the patient's clinical history and type and dates of treatment were recorded along with clinical details surrounding the hemorrhage. The interval between the last treatment and a macular hemorrhage as well as the interval between the last stable examination and a macular hemorrhage were recorded. Visual acuity was recorded for the last visit before an event and at the most recent visit on follow-up.

Results

Four of 6 patients had baseline vision of 20/200 or better, whereas 2 had vision worse than 20/400 (Table 1). Five eyes were treated with an OCT-guided regimen, whereas one was treated with a "treat and extend" strategy. The average number of injections before the macular hemorrhage was 3.5 (range, 2–6). The average time between the date of the last injection and the macular hemorrhage was 16.8 weeks (range, 7.3–28.9 weeks). The average time between the last stable examination and the macular hemorrhage was 4.2 weeks (range, 1 day to 7.3 weeks). Three of 6 eyes had a macular hemorrhage within 4 weeks of a stable examination. One eye had an OCT showing no fluid on the day before a hemorrhage occurred. Among the 4 patients who had better than 20/200 vision, 2 dropped to 20/200 or worse.

Table 1. Macular Hemorrhage in Neovascular Age-Related Macular Degeneration After Stabilization With Antiangiogenic Therapy

Case No.	Age	Gender	Study Eye	Anticoagulant	No. Injections Before SRH	Examination Findings Before SRH	OCT Findings Before SRH	VA Before SRH	Hemorrhage Size/Location	Weeks Between Last Examination and SRH	Weeks Between Last Injection and SRH	VA at Last Follow-Up
1	87	F	OS	Warfarin	2	Disciform scar with exudative lipid	No SRF or CME	5/400	>12 DA, subfoveal	2.9	11.0	LP
2	88	F	OS	—	6	Atrophic CNV	No SRF or CME	20/60	6 DA, subfoveal	0.1	17.3	3/400
3	75	M	OS	Aspirin	3	Quiescent CNV	No SRF or CME	20/50	1 DA <200 μm from foveal center	3.7	10.0	20/40
4	59	M	OS	—	3	Quiescent CNV	No SRF or CME	20/100	>12 DA, subfoveal	6.3	28.9	20/200
5*	95	F	OS	Aspirin, Warfarin	3	Quiescent CNV, no fluid or blood	No SRF or CME, small extrafoveal PED	20/50	2.5 DA, extrafoveal	7.3	7.3	20/60
6	76	M	OD	Clopidogrel	4	Disciform scar, no hemorrhage	No SRF or CME	10/400	3.4 DA within arcades	5.0	26.0	20/400

*Treat and extend regimen.
SRH, subretinal hemorrhage; VA, visual acuity; F, female; M, male; OS, left eye; OD, right eye; CNV, choroidal neovascularization; SRF, subretinal fluid; CME, cystoid macular edema; PED, pigment epithelial detachment; DA, disk areas.

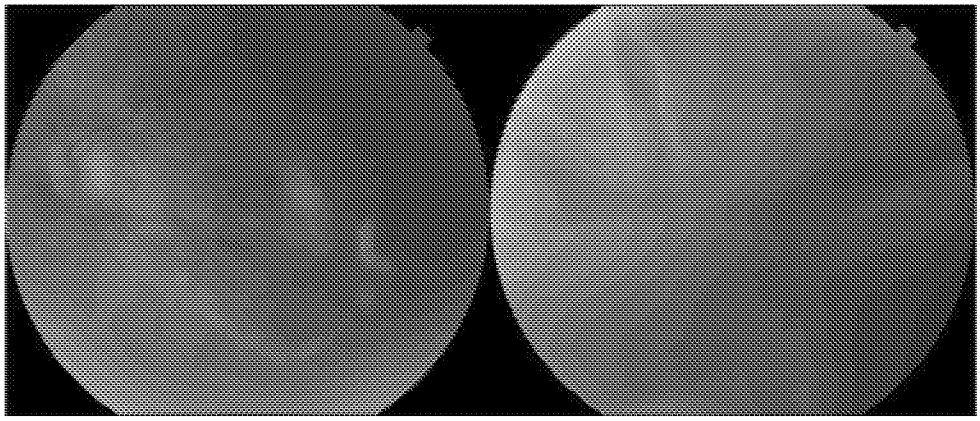


Fig. 1. Case 1. Left, Color photograph of patient 1 showing a quiescent fibrovascular scar secondary to neovascular AMD. Right, Photograph of the same eye 2 weeks later showing a bullous retinal detachment secondary to a massive subretinal hemorrhage.

Case 1

Patient 1 was an 87-year-old woman with a history of advanced neovascular AMD in the left eye for 5 years and a longstanding disciform scar in the right eye. The patient had bilateral 2+ nuclear sclerotic cataracts. She was using latanoprost once daily in the right eye for glaucoma. The patient's medical history included hypertension. She was on warfarin for carotid stenosis. The patient began intravitreal ranibizumab (0.5 mg/0.05 mL) therapy in her left eye for chronic subretinal fluid and a recent small subretinal hemorrhage in the macula. She received a total of two injections. Five weeks after the second injection, visual acuity was stable at 5/400 in the left eye. She was noted to have a quiescent fibrotic choroidal neovascular membrane with no clinically apparent hemorrhage and no fluid detected on OCT (Figure 1, left). Twenty days later, the patient returned with pain and tearing in the left eye for 3 days. On presentation, the patient's visual acuity was light perception in the left eye. Intraocular pressures were 19 in the right eye and 58 in the left eye. Gonioscopy showed a closed angle for 360° in the left eye. Funduscopic examination showed a massive subretinal hemorrhage in the left eye (Figure 1, right). The patient was placed on dorzolamide/timolol and brimonidine drops and acetazolamide (500 mg) orally twice a day to lower the intraocular pressure. A laser iridotomy was performed the next day. Three days later, visual acuity in the left eye remained light perception and the intraocular pressure was 10. There was no view to the posterior pole, but a subretinal and vitreous hemorrhage was evident on B-scan ultrasonography. One month later, the vision was still light perception, and there was persistent subretinal and vitreous hemorrhage.

Case 2

Patient 2 was an 87-year-old woman with neovascular AMD in both eyes. The right eye had a longstanding disciform scar. The left eye received 3 monthly intravitreal injections of bevacizumab (1.25 mg/0.5 mL) for subretinal hemorrhage associated with poorly defined subfoveal choroidal neovascularization. She was monitored for 6 months without additional treatment but later developed a recurrence of subretinal hemorrhage and received 2 additional injections of intravitreal ranibizumab. Four months after her second ranibizumab injection, she was seen for a routine follow-up examination. Visual acuity was counting fingers in the right eye and 20/60 in the left eye. Clinical examination revealed a stable disciform scar in the right eye and pigmentary changes in the left eye without hemorrhage or fluid detected on OCT (Figure 2, left). One day later, she presented with acute loss of vision in the left eye. On examination, visual acuity in the left eye was 20/400. The patient was noted to have a new subfoveal hemorrhage (Figure 2, right). The patient received 4 more intravitreal ranibizumab injections over the next 6 months, but visual acuity remained 3/400. The most recent examination of the left eye revealed a stable fibrotic scar with no hemorrhage or fluid seen clinically and no fluid on OCT.

Case 3

Patient 3 was a 68-year-old man with a history of neovascular AMD in the right eye. His left eye was treated with verteporfin photodynamic therapy followed by 3 monthly injections of intravitreal ranibizumab (0.5 mg/0.5 mL). On examination, 4 weeks after the third injection, visual acuity was 20/800 in the right eye and 20/40 in the left eye. Clinical examination showed a stable disciform scar in the right eye and a small stable area of subretinal fibrosis in the left eye. Fluorescein angiography in the left eye showed no active leakage in the left eye, and OCT in the left eye showed no retinal fluid. The patient returned 5 weeks later with decreased vision in the left eye with

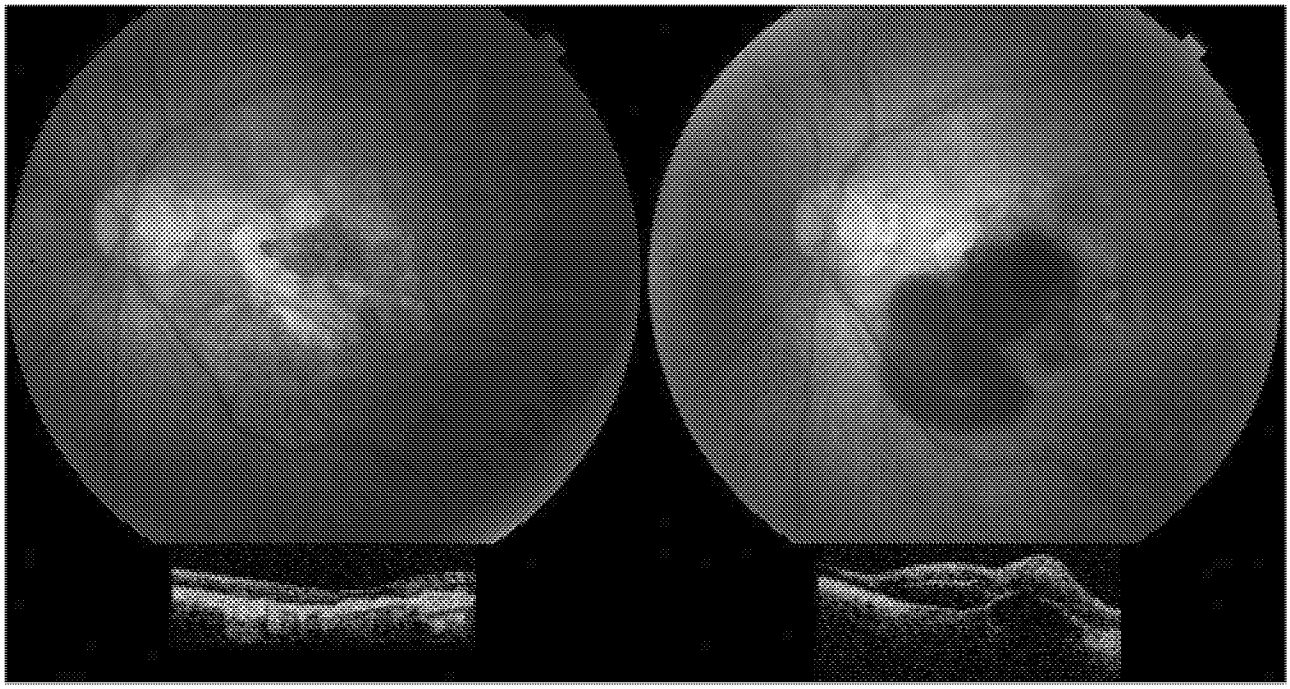


Fig. 2. Case 2. Top and bottom left, Color photograph and OCT of patient 3 demonstrating an absence of subretinal hemorrhage and fluid. Top right, Color photograph of the same eye 1 day later demonstrating subfoveal hemorrhage. Bottom right, OCT demonstrates new subretinal and subretinal pigment epithelium fluid.

a central gray scotoma. Visual acuity was 20/800 in the right eye and 20/100 in the left eye. Clinical examination showed new subretinal blood in the left eye with new retinal fluid on OCT. The hemorrhage and fluid resolved after two monthly intravitreal ranibizumab injections. During a follow-up visit 6 weeks later, the patient's visual acuity was 20/800 in the right eye and 20/50 in the left eye with no clinical evidence of macular hemorrhage or fluid on OCT (Figure 3, left). Based on these findings, no further treatment was given. On examination 4 weeks later, the vision had dropped to 20/125 in the left eye and subretinal hemorrhage and fluid were observed on clinical examination in the left eye (Figure 3, right). The patient was then placed on a maintenance regimen with intravitreal injections of ranibizumab given at intervals of every 5 to 6 weeks. He received 5 additional intravitreal injections of ranibizumab over the next 7 months. At last follow-up, visual acuity had improved to 20/40 in the left eye with no recurrence of macular hemorrhage or fluid on OCT.

Discussion

Intravitreal ranibizumab and bevacizumab have transformed the prognosis for patients with neovascular AMD.[8] Although the optimal dosing regimen of these agents remains uncertain, current treatment algorithms are largely based on the phase IIIb MARINA and ANCHOR trials of ranibizumab in which patients received continuous monthly injections for 2 years.[1–5] Because monthly visits and injections are costly to the healthcare system and difficult to maintain in this elderly patient population, alternative dosing strategies continue to be explored. In the PIER trial of ranibizumab, an initial gain in visual acuity with three monthly injections was lost when patients were switched from monthly injections to quarterly injections as was mandated by the study protocol.[9] This decline in visual acuity was presumably the result of recurrent neovascular activity and associated exudation occurring between injections. More recently, the PrONTO study, using an as-needed dosing regimen guided by monthly eye examinations and OCT, demonstrated visual outcome data similar to monthly dosing. In this small nonrandomized trial, the total number of patient visits remained the same, but the number of injections was reduced by approximately half. The PrONTO strategy is based on the assumption that fluid in the macula will occur before sight-threatening macular hemorrhages and that treating after fluid recurs, rather than before, will give visual results similar to monthly maintenance injections.[5,7]

A recent analysis of the ANCHOR, MARINA, and PIER data demonstrated that monthly intravitreal

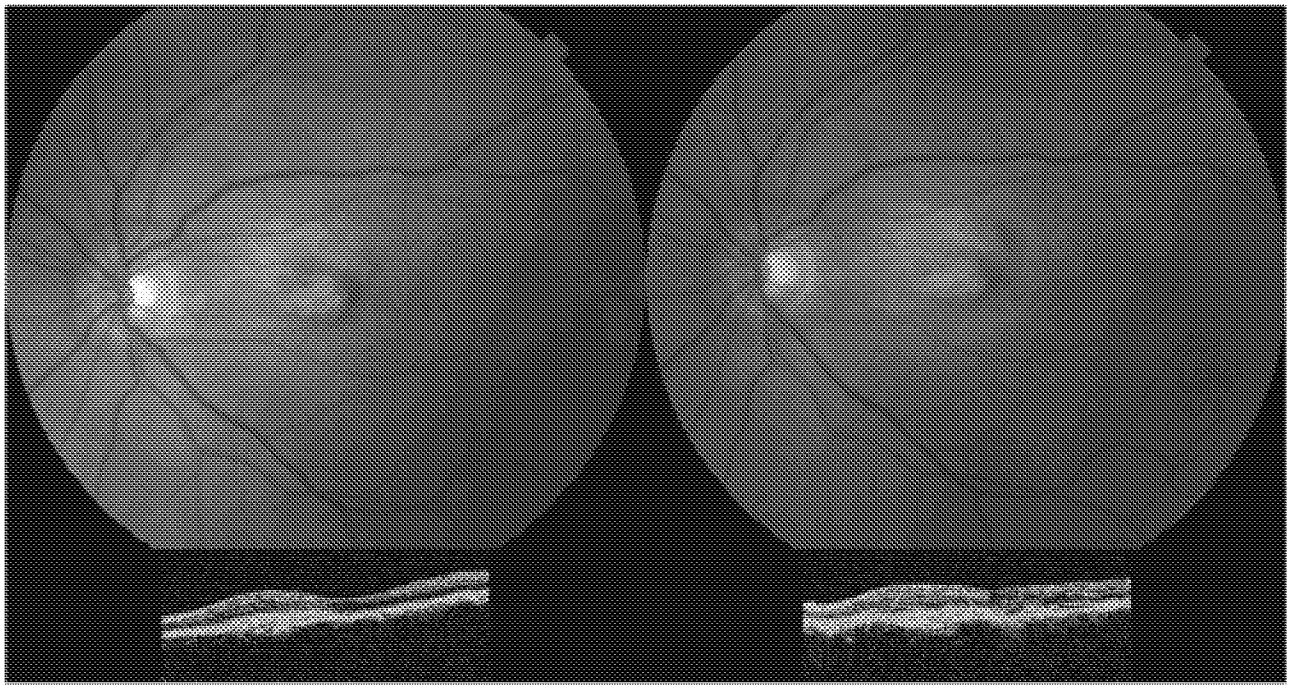


Fig. 3. Case 3. Top and bottom left, Color photograph and OCT of patient 4 demonstrating a quiescent subfoveal fibrovascular scar. Top right, Photograph of the same eye 1 month later showing new subretinal hemorrhage. Bottom right, OCT showing increased retinal thickness temporally.

ranibizumab dosing significantly reduced the frequency of macular hemorrhages compared with the sham controls or photodynamic therapy-treated patients regardless of lesion type. The effect was lost when patients were switched from monthly to quarterly dosing in the PIER study.[10] Reducing the frequency of injections should, therefore, be done with caution.

In our case series, 3 of 6 eyes on intravitreal anti-VEGF therapy developed a sight-threatening macular hemorrhage within 4 weeks of a stable clinical examination and OCT showing an absence of intra- or subretinal fluid. We based our definition of a sight-threatening macular hemorrhage on its size and proximity to the fovea rather than on vision loss per se, although three of our patients had a drop in vision from the hemorrhage. We felt it appropriate to include "near-miss" hemorrhages even if they were not subfoveal or resulted in vision loss. The visual significance of hemorrhagic events is likely influenced by multiple factors such as their size, thickness, proximity to the fovea, and the manner in which they are managed.[11] Hemorrhage size and proximity to the fovea seem to correlate with worse visual outcome in our series (Table 1).

For some patients, a monthly examination schedule similar to the PrONTO strategy may be sufficient to detect early recurrence and allow for timely treatment as needed with fewer treatments than a monthly dosing regimen. However, our findings related to the timing and severity of macular hemorrhages in three of our patients challenge the strategy of treating all patients in this manner. A maintenance regimen may be more appropriate for eyes identified as high risk, in particular eyes with preserved foveal function and patients with poor vision in the fellow eye.

Tilanus et al[12] identified warfarin use as a risk factor for massive intraocular hemorrhage in AMD and noted a possible association between massive hemorrhage and antiplatelet therapy. In our study, 4 of 6 patients were on anticoagulants, 2 were on Coumadin, one was on aspirin, and one was taking clopidogrel. The significance of these agents is uncertain because we do not know the prevalence of anticoagulation use in our general AMD population.

In our study, one patient underwent the "treat and extend" regimen, whereas the other five were treated as needed, based on examination and OCT results. Data on "treat and extend" are limited and primarily based on anecdotal evidence. Furthermore, it is difficult to determine in advance how far one can safely extend a patient's treatment interval without risking a macular hemorrhage. For our patients, the interval between the last injection and an event ranged from 7.3 to 28.9 weeks. A fluorescein angiography may be useful when monitoring patients who are 8 to 10 weeks past their last treatment, especially if considering increasing their interval of retreatment.

Because this is a retrospective case series without a control group, any conclusions should be appropriately restricted. Given the small size of this series, we were unable to draw meaningful conclusions regarding specific lesion characteristics such as neovascular subtype, lesion size, or presence of subretinal fibrosis that would predispose to these hemorrhagic events. Cross-sectional study comparison is also limited because, unlike the phase IIIb ranibizumab trials, we included eyes with vision worse than 20/400, lesions greater than 12 disk areas, and eyes with significant areas of subretinal fibrosis. We also included patients treated with either intravitreal bevacizumab or ranibizumab. Despite these limitations, we feel these cases represent a significant cohort encountered in clinical practice and provide useful information that can be applied to a broader AMD population.

As the PrONTO study has demonstrated, an as-needed treatment regimen based on the clinical status of the individual patient can be an effective strategy with fewer treatments than a monthly dosing regimen. For some patients, however, a sight-threatening macular hemorrhage can occur without the presence of preceding fluid on OCT performed as recently as 1 day before the event. Prophylactic maintenance therapy may be appropriate in some cases.

Key words: age-related macular degeneration, bevacizumab, choroidal neovascularization, ranibizumab, subretinal hemorrhage.

References

1. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444.
2. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
3. Stone EM. A very effective treatment for neovascular macular degeneration. N Engl J Med 2006;355:1493–1495.
4. Rosenfeld PJ, Rich RM, Lalwani GA. Ranibizumab: phase III clinical trial results. Ophthalmol Clin North Am 2006;19:361–372.
5. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am J Ophthalmol 2007; 143:679–680.
6. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006; 113:363–372.e5.
7. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007; 143:566–583.
8. Steinbrook R. The price of sight—ranibizumab, bevacizumab, and the treatment of macular degeneration. N Engl J Med 2006;355:1409–1412.
9. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–248.
10. Barbazetto et al. Dosing regimen and the frequency of macular hemorrhages in neovascular age-related macular degeneration treated with ranibizumab. Presented at the Annual Meeting of the Retina Society; September 2008.
11. Scupola A, Coscas G, Soubrane G, Balestrazzi E. Natural history of macular subretinal hemorrhage in age-related macular degeneration. Ophthalmologica 1999;213:97–102.
12. Tilanus MA, Vaandrager W, Cuypers MH, Verbeek AM, Hoyng CB. Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2000;238: 482–485.

HEMORRHAGIC RECURRENCE OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION NOT PREDICTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY

Ron Margolis, MD, K. Bailey Freund, MD

Purpose: To report a case in which a patient with neovascular age-related macular degeneration developed a large submacular hemorrhage 2 days after spectral domain optical coherence tomography imaging, which revealed no intra- or subretinal fluid.

Methods: A noninterventional case report.

Results: A 93-year-old woman with neovascular age-related macular degeneration was seen for a regular follow-up examination 3 years after treatment with verteporfin photodynamic therapy in which lesion quiescence was achieved. Visual acuity was stable at 20/200, and spectral domain optical coherence tomography scans using 2 different instruments revealed no intra- or subretinal fluid. Two days after clinical examination and imaging, the patient presented with a large submacular hemorrhage and 5/400 vision.

Conclusion: Hemorrhagic exudation from choroidal neovascularization in age-related macular degeneration may occur suddenly, even in the absence of fluid detected by spectral domain optical coherence tomography.

RETINAL CASES & BRIEF REPORTS 4:1–4, 2010

From the Vitreous Retina Macula Consultants of New York, New York, New York.

Advances in the treatment of neovascular age-related macular degeneration (AMD) have included photodynamic therapy (PDT) and the intravitreal antivascular endothelial growth factor (VEGF) drugs such as bevacizumab and ranibizumab.[1-4] In the TAP[1] and VIP[2] studies, patients received treatment with PDT if fluorescein angiography showed leakage from choroidal neovascularization (CNV). In contrast, in the ANCHOR[3] and MARINA[4] trials, patients were treated with intravitreal ranibizumab monthly for 2 years regardless of CNV activity. Because of the burden of monthly injections, additional studies have looked at alternative dosing strategies with the intention of reducing the number of treatments without compromising visual results. In the PIER trial,[5] when patients were switched from monthly to quarterly injections of ranibizumab, they subsequently lost the vision they had gained with monthly injections. However, the PrONTO trial[6] demonstrated that a variable dosing regimen using optical coherence tomography (OCT) as a guide for retreatment could potentially achieve the same visual results as monthly injections but with fewer treatments.[7] Another commonly used dosing regimen referred to as "treat and extend" is also guided by the presence of intra- or subretinal fluid on OCT. With this strategy, the time interval between injections is gradually extended as long as no fluid is seen (J. P. Levine et al, unpublished data). There have been questions of whether OCT is always a reliable measure of neovascular activity. For instance, OCT provides little information regarding the size of neo-

Supported by The Macula Foundation, Inc. and the Heed Fellowship (to R.M.).

The authors have no proprietary interest to report.

Reprint requests: K. Bailey Freund, MD, Vitreous Retina Macula Consultants of New York, 460 Park Avenue, 5th Floor, New York, NY 10022; e-mail: kbfnyf@aol.com

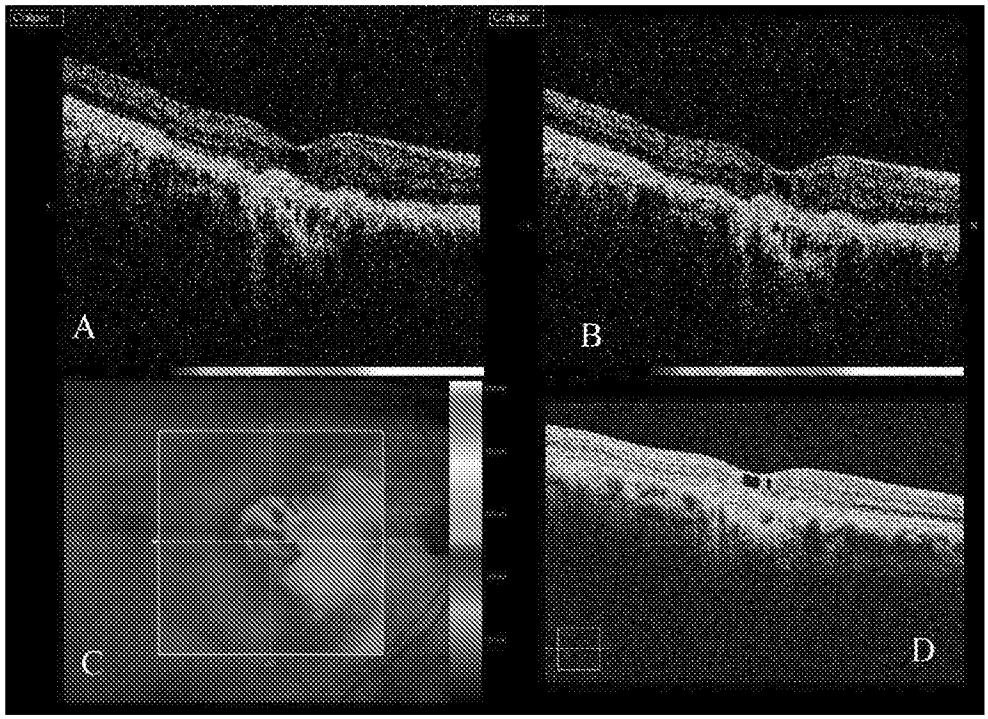


Fig. 1. Optical coherence tomography scan through the right fovea with the Topcon 3D-OCT 1000 (**A** and **B**) and Cirrus HDOCT (**C** and **D**) showing a chronic intraretinal cavitary space with no subretinal fluid.

vascular lesions and cannot differentiate certain lesion components such as polypoidal neovascularization or subretinal fibrosis from actively proliferating well-defined Type 2 (subretinal) neovascularization. With these concerns in mind, we report a patient with neovascular AMD, stable for 3 years after PDT, who developed a large submacular hemorrhage 2 days after a clinical examination, and spectral domain OCT revealed stable findings and no intra- or subretinal fluid.

Case Report

In September 2005, a 90-year-old woman presented with bilateral neovascular AMD. There was a history of hypertension controlled with enalapril. She was not taking aspirin or any other anticoagulants. Visual acuities were 20/400 and 20/200 in the right and left eyes, respectively. Fluorescein angiography showed bilateral Type 3 neovascularization (retinal angiomatous proliferation) of less than 1 disk diameter in size. Two bilateral verteporfin PDT treatments combined with intravitreal triamcinolone acetonide injections were performed in each eye. After treatment, the right eye stabilized with no recurrent angiographic leakage or fluid noted on OCT. The left eye experienced continued exudation and was treated with multiple intravitreal injections of anti-VEGF agents, including bevacizumab and ranibizumab. On a routine evaluation 3 years after the second PDT treatment, visual acuity was 20/200 bilaterally with a small area of clinically inactive, subfoveal subretinal fibrosis in the right eye. There was no fluid, lipid, or hemorrhage detected clinically or on fundus photography.

A small amount of subretinal fluid overlying a similar lesion was noted in the left eye. High-density 6 × 6-mm raster scans were performed centered on the fovea with a resolution of 512 × 128 A-scans using 2 different spectral domain OCT instruments: Cirrus HD-OCT (Model 3000, Carl Zeiss Meditec, Dublin, CA) and the Topcon 3D-OCT 1000 (Topcon, Tokyo, Japan). In addition, 5 high-resolution (4096 A-scan) horizontal line scans centered at the fovea were performed on the Cirrus HD-OCT unit. Foveal thickness in the right eye measured 139 μm on the Topcon instrument, which was unchanged from the measurement of 141 μm on the patient's visit 10 weeks earlier. Review of all OCT cuts revealed a stable, small, focal intraretinal cavitary space in the right eye (Figure 1). This space was not considered to represent active leakage but rather loss of retinal tissue, because reduced retinal thickness and loss of the nuclear and plexiform layers were seen on OCT; it was unchanged from multiple prior OCT scans during a 3-year period, including the prior visit, and there was no leakage on previous fluorescein angiography. The left eye was retreated with intravitreal ranibizumab for a small amount of subretinal fluid detected on OCT. Two days later, the patient returned with rapidly worsening vision in the right eye. Visual acuity was 5/400, and examination revealed a large submacular hemorrhage consistent with recurrence of CNV (Figure 2).

Discussion

The advent of PDT and antivasogenic treatments for neovascular AMD has greatly improved visual outcomes compared with thermal laser photocoagulation. However, the best criteria to use for retreatment remain uncertain. Using OCT to assess CNV activity and direct treatment has become a common approach in the management of neovascular AMD, in part because of the noninvasive nature of this form of imaging and the ease and speed of obtaining this data. Also, unlike fluorescein angiography, in which interpreta-

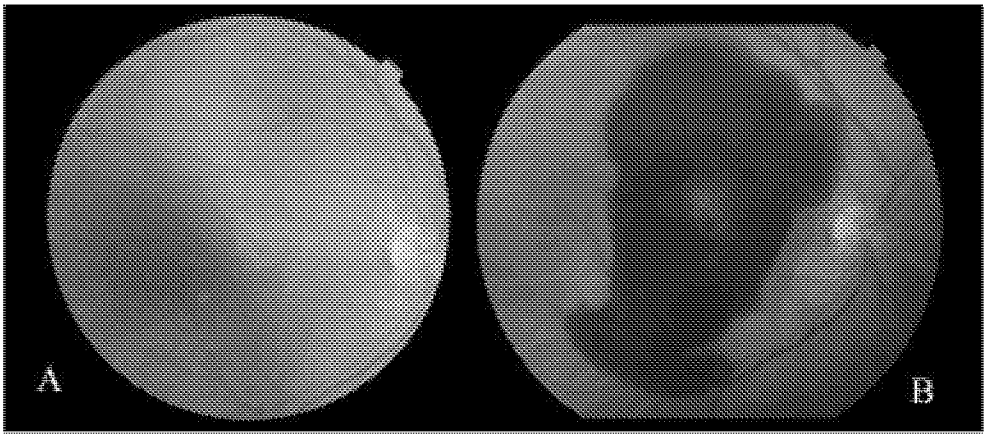


Fig. 2. Color photographs of the right eye showing a small area of clinically inactive subfoveal fibrosis (**A**) 2 days before development of a large submacular hemorrhage (**B**).

tion is often based on subjective interpretations, OCT technology provides quantitative measures of retinal thickness and subretinal fluid. The retreatment criteria chosen for the PrONTO trial were largely based on a clinical impression that OCT could detect the earliest signs of recurrent fluid in the macula (macular cysts or subretinal fluid) after the ranibizumab injections were stopped.[6] However, even in the PrONTO trial, two of the four criteria for retreatment required no OCT guidance: appearance of new classic CNV and new-onset hemorrhage. These elements accounted for 20% of the reinjections performed in this study. The TAP and VIP trials of verteporfin PDT were performed before the widespread use of OCT technology, and retreatment guidelines relied on fluorescein angiographic evidence of leakage.[1,2] High-resolution OCT is reported to have almost 100% sensitivity for cystoid macular edema and almost always correlates with leakage seen on fluorescein angiography.[8-10] However, a discrepancy between OCT and angiography in the detection of macular edema has been reported in up to 5% of cases.[10] Eter and Spaide[11] reported that some patients who had PDT for neovascular AMD had leakage by fluorescein angiography that did not correspond to any observable fluid on OCT. It is, therefore, conceivable that both OCT instruments used in our patient failed to detect early changes that may have predicted the submacular hemorrhage that occurred.

The PrONTO trial demonstrated visual outcome data similar to the MARINA and ANCHOR trials of ranibizuamb while reducing the total number of injections by ~50%. It is potentially significant that most clinical practices deviate from the rigorous testing of visual acuity with the Early Treatment Diabetic Retinopathy Study chart as was used in the PrONTO study. Clinicians have taken the PrONTO results a step further and are commonly implementing a "treat and extend" strategy. In this regimen, the time interval between examinations and intravitreal injections is gradually increased by 1- to 2-week increments as long as there are no signs of reexudation either clinically or on OCT. This interval is gradually extended to a maximum of 8 weeks to 12 weeks with the goal of finding a stable maintenance interval that keeps the macula "fluid-free."

When treating patients on an "as-needed" basis with either anti-VEGF monotherapy or combination approaches, we observed a subset of patients who experienced recurrent exudation with submacular hemorrhage shortly after a stable eye examination in which the Stratus OCT (Carl Zeiss Meditec) did not detect fluid before the event (J. P. Levine et al, unpublished data). Although angiography was not performed, the presence of a large submacular hemorrhage implied active CNV. This finding suggested that we were missing fluid present in the intervals between the six radial cuts that are often used with the time-domain Stratus OCT device. The current report demonstrates that severe recurrent hemorrhagic exudation can occur shortly after imaging showing absence of fluid detected with the much higher resolution and scan densities of the new spectral domain OCT technology. This is particularly concerning given that recurrent exudation after discontinuation of intravitreal anti-VEGF therapy is to be expected. Also, as many as 33% of eyes previously treated with PDT will have a recurrence of CNV within 18 months after their last treatment.[12] Perhaps there are certain patients such as those with preserved foveal function, juxtafoveal lesions, or poor vision in the fellow eye who would do better on a maintenance regimen even in the absence of fluid detected by OCT to reduce the risk of sudden and catastrophic recurrences. However, even with monthly dosing of ranibizumab, loss of visual acuity occurred in 5% to 10% of patients in the ANCHOR and MARINA studies. There are currently no published prognostic factors that are used to identify

patients at high risk for treatment failure, and there is no way to predict whether anti-VEGF treatment would have prevented the submacular hemorrhage that occurred in our patient.

The case presented highlights two important limitations to our current understanding of the pathophysiology of neovascular AMD and its optimal treatment. First, what is the earliest sign of CNV recurrence, and how is it best detected? Although OCT is currently used to detect fluid and direct treatment, other factors such as visual acuity or angiography may be more predictive in certain patients. Second, should treatment be administered only if CNV activity is detected or should maintenance therapy be given even without signs of neovascular activity? Future studies may help answer these questions and identify patients who are at risk for CNV recurrence.

Key words: age-related macular degeneration, optical coherence tomography, recurrence, submacular hemorrhage.

References

1. Bressler NM, Bressler SB, Haynes LA, et al. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: four-year results of an open-label extension of 2 randomized clinical trials: TAP Report No. 7. Arch Ophthalmol 2005;123:1283–1285.
2. Barbazetto I, Burdan A, Bressler NM, et al; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group; Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment–TAP and VIP report No. 2. Arch Ophthalmol 2003;121:1253–1268.
3. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444.
4. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
5. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age related macular degeneration: PIER study year 1. Am J Ophthalmol 2008;145:239–248.
6. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143:566–583.
7. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am J Ophthalmol 2007;143:679–680.
8. Massin P, Girach A, Erginay A, Gaudric A. Optical coherence tomography: a key to the future management of patients with diabetic macular oedema. Acta Ophthalmol Scand 2006;84:466–474.
9. Srinivasan VJ, Wojtkowski M, Witkin AJ, et al. High-definition and 3-dimensional imaging of macular pathologies with high-speed ultrahigh-resolution optical coherence tomography. Ophthalmology 2006;113:2054.
10. Kozak I, Morrison VL, Clark TM, et al. Discrepancy between fluorescein angiography and optical coherence tomography in detection of macular disease. Retina 2008;28:538–544.
11. Eter N, Spaide RF. Comparison of fluorescein angiography and optical coherence tomography for patients with choroidal neovascularization after photodynamic therapy. Retina 2005;25:691–696.
12. Potter MJ, Szabo SM. Recurrence of choroidal neovascularization after photodynamic therapy in patients with age-related macular degeneration. Br J Ophthalmol 2007;91:753–756.

Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study*)

A 12-month, randomized, controlled, double-masked, multicenter phase II study

PASCALE MASSIN, MD, PHD[1]
FRANCESCO BANDELLO, MD, FEBO[2]
JUSTUS G. GARWEG, MD[3]
LUTZ L. HANSEN, MD[4]
SIMON P. HARDING, FRCOPHTH, MD[5]
MICHAEL LARSEN, MD, DMSC[6]
PAUL MITCHELL, MD, PHD[7]
DIANNE SHARP, FRANZCO[8]
U.E.K. WOLF-SCHNURRBUSCH, MD[9]
MARGARITA GEKKIEVA, MD[10]
ANDREAS WEICHSELBERGER, PHD[10]
SEBASTIAN WOLF, MD, PHD[11]

OBJECTIVE — The expression of vascular endothelial growth factor (VEGF) is elevated in diabetic macular edema (DME). Ranibizumab binds to and inhibits multiple VEGF variants. We investigated the safety and efficacy of ranibizumab in DME involving the foveal center.

RESEARCH DESIGN AND METHODS — This was a 12-month, multicenter, sham-controlled, double-masked study with eyes (age >18 years, type 1 or 2 diabetes, central retinal thickness [CRT] ≥300 μm, and best corrected visual acuity [BCVA] of 73–39 ETDRS letters [Early Treatment Diabetic Retinopathy Study]) randomly assigned to intravitreal ranibizumab (0.3 or 0.5 mg; n = 51 each) or sham (n = 49). The treatment schedule comprised three monthly injections, after which treatment could be stopped/reinitiated with an opportunity for rescue laser photocoagulation (protocol-defined criteria). After month 1, dose-doubling was permitted (protocol-defined criteria, injection volume increased from 0.05 to 0.1 ml and remained at 0.1 ml thereafter). Efficacy (BCVA and CRT) and safety were compared between pooled ranibizumab and sham arms using the full analysis set (n = 151, patients receiving ≥1 injection).

RESULTS — At month 12, mean ± SD BCVA improved from baseline by 10.3 ± 9.1 letters with ranibizumab and declined by 1.4 ± 14.2 letters with sham (P < 0.0001). Mean CRT reduction was 194.2 ± 135.1 μm with ranibizumab and 48.4 ± 153.4 μm with sham (P < 0.0001). Gain of ≥10 letters BCVA from baseline occurred in 60.8% of ranibizumab and 18.4% of sham eyes (P < 0.0001). Safety data were consistent with previous studies of intravitreal ranibizumab.

CONCLUSIONS — Ranibizumab is effective in improving BCVA and is well tolerated in DME. Future clinical trials are required to confirm its long-term efficacy and safety.

Diabetes Care 33:2399–2405, 2010

From the [1]Assistance Publique des Hôpitaux de Paris, Ophthalmology Department, Hôpital Lariboisière, Paris, France; the [2]Department of Ophthalmology, University of Udine, Udine, Italy; the [3]Clinic for Vitreoretinal Disease, Swiss Eye Institute and University of Bern, Bern, Switzerland; the [4]University Hospital Freiburg, Freiburg, Germany; the [5]Ophthalmology Research Unit, School of Clinical Sciences, University of Liverpool, Liverpool, U.K.; the [6]Department of Ophthalmology, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark; the [7]Centre for Vision Research, University of Sydney, Sydney, New South Wales, Australia; the [8]Department of Ophthalmology, University of Auckland, Auckland, New Zealand; the [9]Bern Photographic Reading Center, Department of Ophthalmology, Inselspital, University Bern, Bern, Switzerland; [10]Novartis Pharma, Basel, Switzerland; and the [11]Department of Ophthalmology, Inselspital, University Bern, Bern, Switzerland.

Corresponding author: Sebastian Wolf, sebastian.wolf@insel.ch.

Received 15 March 2010 and accepted 8 August 2010.

F.B. is currently affiliated with the Department of Ophthalmology, University Vita Salute, Scientific Institute San Raffaele, Milan, Italy.

*A complete list of the RESOLVE investigators can be found in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-0493/DC1.

DOI: 10.2337/dc10-0493. Clinical trial reg. no. NCT00284050, clinicaltrials.gov.

See accompanying editorial, p. 2484.

Diabetes affects >220 million people worldwide (1). Diabetic macular edema (DME) is one of the major causes of visual impairment (VI) in patients with diabetic retinopathy (2,3). With diabetes prevalence estimated to double during the next 20 years (4), in the future it is likely that DME may be responsible for substantial vision loss unless treated adequately.

Laser photocoagulation is the mainstay of DME treatment; it reduces the risk of moderate vision loss by ~50%, with 3% of eyes showing vision improvement (≥3 lines), but a substantial proportion of treated eyes remain unresponsive (5). In a recent report of a 2-year study, focal/grid laser photocoagulation was more effective and had fewer side effects than intravitreal triamcinolone acetonide (6). Pars plana vitrectomy is another treatment modality investigated for DME; however, both intravitreal triamcinolone acetonide and pars plana vitrectomy have limited efficacy and/or significant side effects (7,8).

There is currently a significant unmet medical need for an effective DME treatment that not only stabilizes but improves and maintains vision and has a better safety profile than the available DME treatment options. Several proinflammatory cytokines including vascular endothelial growth factor (VEGF) have been shown to be extensively involved in the development and progression of DME (9). VEGF promotes neovascularization and microvascular leakage (10). Thus, inhibiting VEGF may provide an alternative therapeutic approach in DME. Anti-VEGF agents have been extensively investigated in neovascular age-related macular degeneration (nAMD). Given that anti-VEGF drugs delivered within the vitreous could pass into the systemic circulation, VEGF inhibition could in turn produce systemic adverse effects, which may be potentially serious for diabetic patients (11). Therefore, randomized clinical trials are required to establish both the efficacy and systemic adverse effects in this population.

Ranibizumab is a fully humanized

monoclonal antibody fragment (Fab), which binds to multiple variants of VEGF-A (12), and is approved for the treatment of nAMD. In a pilot study (10 patients with DME), ranibizumab was effective and well tolerated in maintaining or improving best-corrected visual acuity (BCVA) and in reducing central retinal thickness (CRT) (13). The 6-month Ranibizumab for Edema of the Macula in Diabetes (READ-2) study (phase II) was the first to compare the efficacy of ranibizumab with laser photocoagulation or a combination of both in patients with VI due to DME; ranibizumab led to significant improvements in mean BCVA (7.2 letters) compared with laser photocoagulation (−0.4 letters) or the combination (3.8 letters) (14). Studies in DME have also been conducted with other anti-VEGF agents, pegaptanib and bevacizumab (15–19). Initial results from these studies are encouraging in some patients with DME; further prospective randomized clinical trials may confirm their effects in DME.

We report the results of the phase II RESOLVE study in patients with VI due to DME. This study evaluated the efficacy and safety of ranibizumab compared with sham treatment over 12 months.

RESEARCH DESIGN AND METHODS

Inclusion and exclusion criteria

Patients (aged >18 years) with type 1 or 2 diabetes and DME were eligible if they had a visual acuity between 20/40 and 20/160, CRT ≥300 μm, HbA1C ≤12%, decreased vision attributed to foveal thickening from DME, that was not explained by any other cause, and clinically significant DME in at least one eye confirmed by a central reading center (Bern Photographic Reading Centre, University Bern, Bern, Switzerland) using stereoscopic fundus photographs, fluorescein angiography, and optical coherence tomography (OCT) (Stratus OCT; Carl Zeiss Meditec, Jena, Germany). Eyes were deemed eligible if, in the judgment of the investigator, laser photocoagulation could be safely withheld in the study eye for at least 3 months after random assignment. Patients were excluded if they had unstable medical status including glycemic control and blood pressure or panretinal laser photocoagulation performed within 6 months before study entry, and grid/central laser photocoagulation was excluded except for patients with only mild laser burns at least 1,000 μm from the center of the fovea performed >6 months preceding day 1. Details are found in supplementary Table 1 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-0493/DC1).

Study design

Of the 207 screened patients, 151 eligible patients were randomly assigned 1:1:1 to either ranibizumab (0.3 mg, $n = 51$ or 0.5 mg, $n = 51$) or sham treatment ($n = 49$) (randomization details are found in the supplementary data, available in an online appendix). Before each scheduled treatment, patients were asked to self-administer a topical antibacterial agent for 3 days. Patients received three monthly ranibizumab (0.3 or 0.5 mg) or sham injections (injection volume 0.05 ml). Thereafter, treatment could be stopped or reinitiated based on treatment success, disease activity, futility, or safety criteria (supplementary Fig. 1, available in an online appendix). It is important to note that the sham arm was a nontreatment arm, and patients did not receive intraocular injections. The sham eyes were locally anesthetized, and pressure with the blunt tip of the syringe (without needle) was applied to the anesthetized surface of the eye to mimic the injection. After month 1, the ranibizumab dose (or sham) could be doubled by increasing the injection volume from 0.05 to 0.1 ml if CRT remained >300 μm or was >225 μm and the reduction in retinal edema from the previous assessment was <50 μm. Once the injection volume was increased to 0.1 ml, subsequent administrations remained at 0.1 ml (0.6 or 1.0 mg ranibizumab). If treatment had been withheld for >45 days, subsequent injections restarted with the initial injection volume of 0.05 ml. Because of this possibility of dose doubling, the ranibizumab treatment groups are referred to as "0.3–0.6 mg" and "0.5–1.0 mg."

The study included a planned interim analysis at month 6 to facilitate early decisions on dose, treatment ratio, sample adjustments, or futility assessments (details are available in the supplementary data). Here, we present the overall pooled efficacy and safety of ranibizumab (pooled 0.3–0.6 mg with 0.5–1.0 mg) versus sham treatment (by-dose data are found in the supplementary data). The primary end point was the mean average change in BCVA from baseline to month 1 through month 12 (chosen as the primary end point because it is less sensitive to monthly variations and reflects the treatment impact over the entire treatment period). Secondary end points included mean change in BCVA and CRT from baseline to month 12, categorized BCVA outcome, and safety.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, Good Clinical Practice, and applicable regulatory requirements. The research protocol and its amendments were approved by relevant institutional review boards and ethics committees from the respective study centers, and all participants gave written informed consent.

Assessments

BCVA and CRT were assessed by certified examiners using Early Treatment Diabetic Retinopathy Study (ETDRS) standardized protocols and OCT, respectively, at scheduled visits. Safety (ocular, nonocular, or systemic) and vital signs (including blood pressure [sitting systolic and diastolic]) and serum levels of HbA1C were assessed at each scheduled monthly visit. The occurrence of adverse events (AEs) was sought by nondirective questioning of the patient at each visit, and these were also recorded when reported by the patient during or between visits or through physical examination, laboratory test, or other assessments. Serious adverse events (SAEs) were monitored continuously. Routine hematology and systemic immunoreactivity assessments (i.e., presence of serum antibodies against ranibizumab) were performed at baseline and month 12.

Statistical analysis

The plan was to screen ~225 patients to achieve a sample size of 150 eligible patients within an estimated 12-month recruitment period. The full analysis set (FAS) was the primary efficacy analysis set. FAS comprised all patients who received the study treatment at least once (ranibizumab or sham) and who had at least one post baseline BCVA assessment. The safety population was identical to the FAS.

For the primary efficacy analysis, missing data were imputed using the last observation carried forward (LOCF) method, with alternative missing data handling procedures used for corresponding sensitivity analysis. For statistical hypothesis testing of the mean average changes from baseline in BCVA the stratified Cochran-Mantel-Haenszel test was

used with observed values (permutation tests) as scores (details of the hypothesis testing are available in the supplementary data). StatXact software was used to compute the test.

In addition, the primary efficacy variable was assessed using parametric statistical methods. The two-sided 95% CI for the primary efficacy variable and the corresponding difference in means between treatments were calculated using the least squares means from an ANOVA model with treatment and categories of baseline visual acuity and baseline CRT as factors.

RESULTS

Characteristics of patients

Patients from the ranibizumab and sham arms were comparable with respect to baseline characteristics (supplementary Table 2, available in an online appendix). Less than 20% of patients in all arms had previously received laser photocoagulation for DME. There were more discontinuations in the sham arm than the ranibizumab arm (18.4 and 9.8%, respectively) (supplementary Fig. 2, available in an online appendix).

Treatment characteristics: adjustments and number of treatments

The number of patients whose treatment was interrupted or stopped was comparable between the treatment arms (37 [36.3%] and 20 [40.8%], for ranibizumab and sham, respectively). Most treatment adjustments in the sham arm were made because of a lack of efficacy (17 of 20 [85%] and 9 of 37 [24.3%] for sham and ranibizumab, respectively); conversely, for ranibizumab, they were prompted by improved BCVA and/or reduced CRT (17 of 37 [45.9%] for ranibizumab and none for sham).

The mean ± SD numbers of injections administered during 12 months were 10.2 ± 2.5 and 8.9 ± 3.5 for ranibizumab and sham, respectively. The investigators more frequently undertook dose doubling in the sham arm (45 [91.8%]) than in the ranibizumab arm (70 [68.6%]). Most instances of dose doubling occurred at month 1 (70–78%). A larger proportion of patients in the sham arm received rescue laser photocoagulation than in the ranibizumab-treated arms (17 [34.7%] and 5 [4.9%], respectively); among these patients, most received one to two laser treatments.

Table 1—*Mean BCVA and CRT at month 12*

	Ranibizumab pooled	Sham
N	102	49
BCVA (ETDRS letters)		
Baseline	60.2 ± 9.9	61.1 ± 9.0
Mean average change from baseline to month 1 through month 12		
Average month 1 to month 12	68.0 ± 11.7	61.0 ± 13.9
Average change from baseline	7.8 ± 7.7	−0.1 ± 9.8
Comparison vs. sham		
Difference in least squares means	7.9	—
95% CI for difference	5.0 to 10.9	—
P value	<0.0001	—
Mean change from baseline to month 12		
Month 12	70.5 ± 12.1	59.7 ± 17.3
Change from baseline	10.3 ± 9.1	−1.4 ± 14.2
Comparison vs. sham		
Difference in least squares means	11.9	—
95% CI for difference	8.1 to 15.7	—
P value	<0.0001	—
CRT (μm)		
Baseline	455.4 ± 114.2	448.9 ± 102.8
Month 12	261.2 ± 81.9	400.5 ± 139.2
Comparison vs sham		
Change from baseline	−194.2 ± 135.1	−48.4 ± 153.4
Difference in least squares means	−155.0	—
95% CI for difference	−195.4 to −114.6	—
P value	<0.0001	—
Categorized BCVA outcome, *n* (%)		
Gain of ≥1 letters*	92 (90.2)	27 (55.1)
Gain of ≥10 letters*	62 (60.8)	9 (18.4)
Loss of ≥10 letters*	5 (4.9)	12 (24.5)
Gain of ≥15 letters†	33 (32.4)	5 (10.2)
Loss of ≥15 letters†	3 (2.9)	10 (20.4)

Data are means ± SD unless otherwise indicated. Ranibizumab dose and by group data (A, B, and A + B) are presented in supplementary Tables 3 and 4 (available in an online appendix). *$P < 0.0001$; †$P = 0.0001$. (Test for treatment difference [ranibizumab vs. sham], Cochran-Mantel-Haenszel test is of "general association." Stratified analysis includes baseline visual acuity [≤60 or >60 letters] and baseline CRT [≤400 μm or >400 μm].)

Efficacy

The mean average change in BCVA from baseline to month 1 through 12 (primary end point) was statistically superior with ranibizumab (7.8 letters) compared with sham (−0.1 letters) (least squares means difference 7.9 letters; $P < 0.0001$). At month 12, mean ± SD BCVA improved by 10.3 ± 9.1 letters from baseline with ranibizumab and declined by 1.4 ± 14.2 letters with sham ($P < 0.0001$) (Table 1). Ranibizumab led to a rapid and continuous improvement in mean BCVA, with superior benefits observed as early as month 1 (Fig. 1).

The mean BCVA improvement with ranibizumab treatment over time was paralleled by improvement in mean CRT (Fig. 1). The mean change in CRT from baseline to month 12 was significantly higher in the ranibizumab arm than in the sham arm (−194.2 vs. −48.4 μm, respectively; difference in least squares means, −155 μm, $P < 0.0001$) (Table 1). The impact of therapy on macular edema (fundus photographs and OCT) is illustrated for ranibizumab (0.3–0.6 mg) and sham in the supplementary data. At month 12, 60.8% of the patients receiving ranibizumab gained ≥10 letters of BCVA from baseline compared with 18.4% in the sham arm ($P < 0.0001$). A similar difference was seen in all the other categories (Table 1).

In terms of the ETDRS severity score, the observed change from baseline to month 12 could be analyzed in ~50% of FAS patients. Deterioration within the categories mild-moderate-severe (0–35, 43–47, and ≥53) was observed in 3.9%

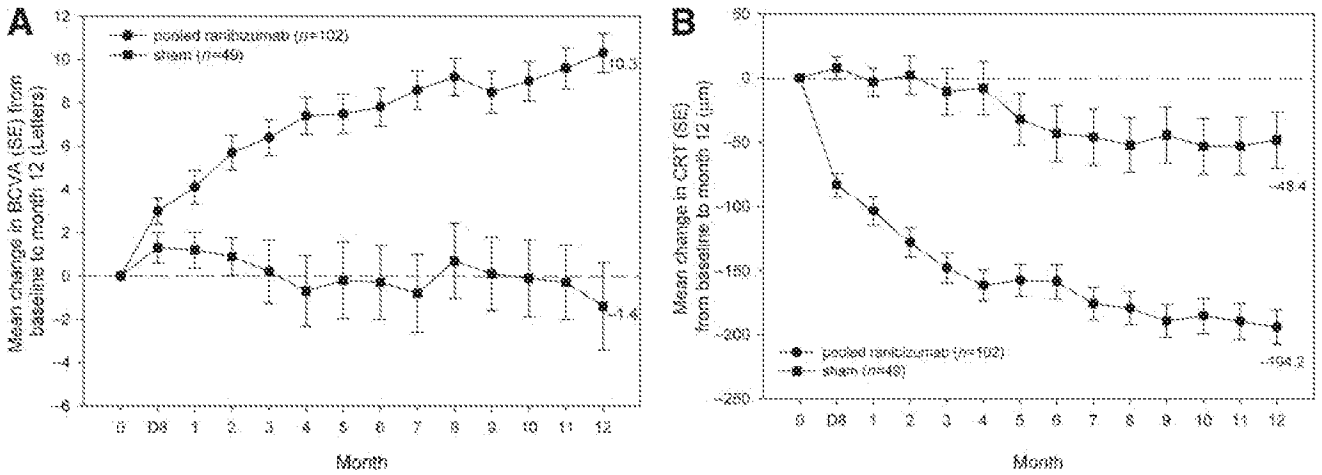


Figure 1—*Mean change from baseline to month 12 in (A) BCVA and (B) CRT of the study eye: data for pooled ranibizumab doses (0.3–0.6 and 0.5–1.0 mg) versus sham. Full analysis set, LOCF. (Ranibizumab by-dose data are found in supplementary Fig. 4A and B, available in an online appendix.)*

(n = 2 of 51) ranibizumab-treated patients, compared with 18% (n = 4 of 22) sham patients. Corresponding relevant improvements were seen in 21.6% (n = 11 of 51) ranibizumab patients, whereas no such improvement occurred in the sham patients.

Safety

There were no imbalances in the rates of ocular and nonocular SAEs or AEs between the ranibizumab and sham arms (Table 2). The proportion of patients with ocular SAEs in the study eye was comparable between the treatment arms (ranibizumab: 4 [3.9%]; sham: 1 [2.0%]). Most of the SAEs were nonocular in origin (ranibizumab: 14 [13.7%]; sham: 8 [16.3%]). There was one occurrence of myocardial infarction (nonocular SAE) with ranibizumab that was suspected to be related to the study drug. One death from urinary bladder cancer was reported with ranibizumab, which was not suspected to be related to the study drug or procedure. Endophthalmitis (n = 2 of 102) and myocardial infarction (n = 1 of 102) led to study drug discontinuation in three patients. The most frequently reported ocular AEs (ranibizumab and sham) were conjunctival hemorrhage, intraocular pressure increase, and eye pain (Table 2). The proportion of patients reporting nonocular AEs was comparable between the ranibizumab and sham arms (64 [62.7%] and 32 [65.3%], respectively).

The incidence of hypertension and arterial thromboembolic events, both possibly due to VEGF inhibition, were comparable between ranibizumab and sham arms (hypertension: 9 [8.8%] and 5 [10.2%]; arterial thromboembolic events: 3 [2.9%] and 2 [4.1%], respectively).

There were no clinically significant differences between treatment arms at baseline for mean serum levels of HbA1C

Table 2—*Most frequent SAEs and AEs over 12 months*

	Ranibizumab pooled	Sham
N	102	49
SAEs		
Ocular SAEs		
Total	4 (3.9)	1 (2.0)
Vitreous hemorrhage*	1 (1.0)	0 (0.0)
Retinal ischemia	1 (1.0)	0 (0.0)
Retinal artery occlusion*	1 (1.0)	0 (0.0)
Endophthalmitis*	2 (2.0)	0 (0.0)
Retinal detachment	0 (0.0)	1 (2.0)
Nonocular SAEs		
Total	14 (13.7)	8 (16.3)
Infections and infestations†	2 (2.0)	3 (6.1)
Urinary bladder cancer	1 (2.0)	0 (0.0)
AEs		
Ocular AEs		
Total	80 (78.4)	28 (57.1)
Conjunctival hemorrhage*	23 (22.5)	7 (14.3)
Eye pain*	18 (17.6)	10 (20.4)‡
Nonocular AEs		
Total	64 (62.7)	32 (65.3)
Nasopharyngitis	10 (9.8)	1 (2.0)
Hypertension	7 (6.9)	4 (8.2)
Potentially related to systemic VEGF inhibition		
Total	14 (13.7)	6 (12.2)
Arterial thromboembolic events§	3 (2.9)	2 (4.1)
Hypertension	9 (8.8)	5 (10.2)
Nonocular hemorrhage	2 (2.0)	0 (0.0)

Data are *n* (%). Additional safety data are presented in supplementary Tables 3, 5, and 6 (available in an online appendix). *Suspected to be related to study drug/procedure. †Infections and infestations include gastroenteritis viral, infected epidermal cyst, cellulitis, diabetic gangrene, and gastroenteritis. ‡One event documented after start of treatment with nonstudy medication (marketed ranibizumab). §Myocardial infarction (1 in sham and ranibizumab), retinal artery occlusion (1 in ranibizumab), transient ischemic attack (1 in ranibizumab), and angina pectoris (1 in sham).

and mean blood pressure (supplementary Table 7, available in an on online appendix). The urine dipstick protein test was performed in 60% of the FAS patients. The deterioration within the categories (categories 1+, 2+, 3+, or greater) was comparable between the ranibizumab and sham groups (22.9% [n = 14 of 61] and 28.5% [n = 8 of 21], respectively), none reported as AEs by the investigators.

The formation of antibodies to ranibizumab was reported in three patients post baseline. One patient in the sham arm showed positive immunoreactivity both at baseline and post baseline.

CONCLUSIONS — Ranibizumab led to significant and continuous improvements in both BCVA and CRT over 12 months compared with sham treatment in patients with VI due to DME. The safety profile of ranibizumab appears to be similar to that reported for its registered use in nAMD. Over the 12-month study period, ranibizumab-treated patients had a mean average gain in BCVA of 7.8 letters compared with baseline, whereas sham patients had a mean average decrease of 0.1 letter. At the end of the 12-month assessment period, ranibizumab led to a mean gain of 10.3 letters from baseline compared with a decline of 1.4 letters in the sham patients. The proportion of patients who gained ≥10 letters as well as ≥15 letters was threefold higher in the ranibizumab arm compared than in the sham arm.

More patients receiving ranibizumab had their dose adjusted because of disease improvement (BCVA and/or CRT), whereas more patients in the sham arm had their dose adjusted because of lack of efficacy. Ranibizumab was well tolerated over 12 months with a safety profile comparable to that observed in prior nAMD studies (20–22). There were no new AEs reported in patients with DME compared with patients with nAMD. The incidence of ocular and nonocular AEs and SAEs was low. There were two cases of endophthalmitis (SAEs) reported in the ranibizumab treatment group (2%). In one patient, this event resulted in study discontinuation, and the event was considered by the investigator to be related to the study procedure. In the second patient, endophthalmitis was considered by the investigator to be related to the study medication (because it recurred on rechallenge). However, this case of endophthalmitis resolved and at study end the patient had a 7-letter BCVA increase compared with baseline. The incidence of endophthalmitis (SAE) in the RESOLVE study (2%) was slightly higher compared with that reported in prior AMD trials (0–1.0%) (23). However, the underlying sample size and the number of events are too small to allow for conclusions regarding the risk of endophthalmitis in patients with DME. A recent analysis of safety in diabetic and nondiabetic patients with AMD from the AMD trials Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR), Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA), Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovasularization with or without Classic CNV Secondary to Age-Related Macular Degeneration (PIER), the Safety Assessment of Intravitreal Lucentis for AMD (SAILOR), EXCITE, and EXTEND I (N = 3,736) has revealed that the incidences of endophthalmitis were comparable between the diabetic (0.4% [2 of 523]) and nondiabetic patients (0.5% [17 of 3,213]) with AMD, with no indication of increased risk for the diabetic population (24). As in prior nAMD studies eye pain, conjunctival hemorrhage, and transient intraocular pressure increase were the most frequently reported ocular AEs, and these were suspected to be related to study procedure (ocular injection).

One of the limitations of this study was that there was no laser control arm, but laser photocoagulation was permitted as rescue therapy (starting month 3). Approximately 5% ranibizumab and 35% sham patients received laser photocoagulation during the study. Furthermore, the impact of rescue laser treatment on BCVA outcome was not assessed.

When patients were enrolled, we were aware that the study required deferral of laser treatment for 3 months or discontinuation of patients who needed laser photocoagulation within the first 3 months of the study. This is at the border between requiring observation and immediate treatment and we recognize that it is a judgment that balances the relative effectiveness and risk of laser treatment. Examples of the type of eligible clinical scenarios include DME in the presence of stable visual acuity for >3 months; DME associated with leaking microaneurysms, risk of producing symptomatic perifoveal scotomata, choroidal neovascularization or expansion of scarring leading to foveolar atrophy, or borderline reactivation after prior laser treatment. The relatively low number of eyes that received photocoagulation before or after enrollment suggests that eyes in which photocoagulation was not considered a good option were common in this trial. The trial protocol did not include any attempt to guide investigators as to the exact use of laser therapy because it was believed that no satisfactory standard exists for this purpose and that the responsibility had to remain exclusively with the investigator. Approximately 20% of eyes had received prior laser treatment; however, a subgroup analysis revealed that this treatment had no impact on the BCVA outcome. Our results should be interpreted with these factors in mind and may not be applicable to more advanced disease. However, we believe that they are relevant to patients in the intermediate stages of the development of DME.

It is proposed that ranibizumab as an adjunct to laser treatment may be more effective than either therapy alone; in addition, the combination may lead to fewer ranibizumab treatments. The recent Diabetic Retinopathy Clinical Research Network (DRCR.net) study showed that ranibizumab combined with prompt/deferred laser photocoagulation provided superior benefits compared with laser treatment alone in DME (25). However, results from the earlier READ-2 study showed that ranibizumab monotherapy led to superior improvements in BCVA compared with the combination or laser photocoagulation alone (14). The RESTORE study, which assesses the efficacy and safety of 0.5 mg ranibizumab alone or as an adjunct to laser treatment compared with laser treatment, will provide further knowledge of the efficacy and safety of ranibizumab either as monotherapy or as an adjunct to laser therapy.

The RESOLVE study included a possibility of dose-doubling that was eventually undertaken in the majority of patients receiving ranibizumab. Most patients (86%) received a dose between 0.5 and 1.0 mg inclusive during the study period. Dose doubling was included to allow for best efficacy outcomes, however, the study was not designed for precise estimates of the effect of dose doubling. Upon analysis of the actual doses used in each treatment arm over the study period, the average dose received was 0.47 mg in the 0.3–0.6 mg group and 0.76 mg in the 0.5–1.0 mg group. Because these variable

dose changes resulted in a heterogeneous group within treatment arms, with overlapping between treatment arms, the study results were mainly discussed based on the pooled ranibizumab group and are considered to be representative for treatment with 0.5-mg injections.

Given the nature of diabetes and variability in patients with DME with regard to disease progression and vision loss, there is a need for an individualized treatment regimen. The RESOLVE study allowed for such a dosing regimen, because retreatment (after three monthly injections) was based on predefined visual acuity/CRT and safety criteria; this concept partly mimics clinical practice. However, unlike clinical practice, the visual acuity/CRT criteria adopted in the study were stringent to increase the likelihood of patient benefit.

Results from the RESOLVE study indicate that DME responds well to treatment with intravitreal ranibizumab over 1 year. In light of the sustained improvements in BCVA and CRT over the 12-month study period combined with a good safety profile, ranibizumab appears to be a promising pharmacological agent for the management of visual impairment due to DME. These results provide a strong basis for continuing development of ranibizumab in phase III trials in DME, and this study is a stepping stone toward increasing the treatment options for these patients.

Acknowledgments— This study was supported by Novartis Pharma.

P.Ma. has served on advisory boards for Novartis and its competitors and has received honoraria and travel and accommodation payments from them. F.B. has served on advisory boards for Novartis and has received honoraria and travel and accommodation payments from them as well as from Allergan, Pfizer, and Solvay. L.L.H. presented interim data of the study (Macula Update, Leipzig 2008) and has received honoraria and travel and accommodation payments from Novartis. S.P.H. has served on advisory boards for Novartis and its competitors and has received honoraria and travel and accommodation payments from them. M.L., on behalf of his employer, has performed contract research and consultancy services for Novartis and its competitors, including serving on advisory boards. P.Mi. has received a consultancy fee from Novartis Pharma, Pfizer, Solvay, and Allergan and lecture fees/honoraria and travel and accommodation payments from Novartis Pharma, Pfizer, Solvay, and Allergan. D.S. has served on advisory boards for Novartis and has received honoraria and travel and accommodation payments from them. U.E.K.W.-S., on behalf of her employer, has performed contracted research for Novartis and its competitors. S.W. has received a consultancy fee from Novartis Pharma and lecture fees/honoraria from Novartis Pharma, Pfizer, and Allergan and is an Advisory Board Member for studies sponsored by Novartis as well as several other companies. No other potential conflicts of interest relevant to this article were reported.

P.Ma. assisted with the design of the study, participated in the study as principal investigator, contributed to the collection of research data, contributed to discussion, and reviewed/edited the manuscript. F.B. contributed to the collection of research data and manuscript preparation, and reviewed/edited the manuscript. J.G.G. was principal investigator at the Bern study center, contributed to the collection of research data and manuscript preparation, and reviewed/edited the manuscript. L.L.H. was the principal investigator of the institution with the highest rate of recruitment and reviewed/edited the manuscript. S.P.H. contributed to manuscript preparation and reviewed/edited the manuscript. M.L., P.Mi., D.S. participated as principal investigator, contributed to the collection of research data and manuscript preparation and reviewed/edited the manuscript. U.E.K.W.-S. contributed to data collection and evaluation of imaging data at the Bern Photographic Reading Center and manuscript preparation and reviewed/edited the manuscript. M.G. participated in the study as clinical trial head, contributed to manuscript preparation, and reviewed/edited the manuscript. A.W. was the study statistician, researched data, and contributed to manuscript preparation. S.W. contributed to development of the protocol, supervised reading center activities and data analysis, contributed to manuscript preparation, and reviewed/edited the manuscript.

Parts of this study were presented in abstract form at the annual meeting of the American Academy of Ophthalmology, Atlanta, Georgia, 8–11 November 2008; at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, 3–9 May 2009; at the 45 annual meeting of the European Association for the Study of Diabetes, Vienna, Austria, 29 September–2 October 2009; and at the 27 annual meeting of the American Society of Retinal Specialists, New York, 30 September–4 October 2009.

We thank the following Novartis employees who assisted with the analysis and/or interpretation of these data: Y. Hashad, G. Burian, O. Gerstner, Ch. Ortmann, and S. Osborne. We also thank third parties that assisted in the study conduct: Global Central Labs PPD (Belgium), Bern Reading Center (Switzerland), MEDIDATA (Germany), and VA certifiers B. Bhogal, A. Lea, and K. Burke. Medical writing and editorial support was provided by Aditi Gandhe and Shivani Mittra of Novartis Healthcare, India.

References

1. Diabetes. Fact sheet No. 312 [article online], 2009. Available from http://www.who.int/mediacentre/factsheets/fs312/en/. Accessed 20 December 2009
2. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844–851
3. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology 1998;105:1801–1815
4. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414–1431
5. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985;103:1796–806
6. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;**115**:1447–1449, 1449.e1–10
7. Cekiç O, Chang S, Tseng JJ, Akar Y, Barile GR, Schiff WM. Cataract progression after intravitreal triamcinolone injection. Am J Ophthalmol 2005;139:993–998
8. Thomas D, Bunce C, Moorman C, Laidlaw DA. A randomised controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema. Br J Ophthalmol 2005;89:81–86
9. Aiello LP, Bursell SE, Clermont A, Duh E, Ishii H, Takagi C, Mori F, Ciulla TA, Ways K, Jirousek M, Smith LE, King GL. Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective beta-isoform-selective inhibitor. Diabetes 1997;46:1473–1480
10. Poulaki V. Hypoxia in the pathogenesis of retinal disease. In Retinal Vascular Disease. Joussen AM, Gardner TW, Kirchhof B, Ryan SJ, Eds. Berlin, Germany, Springer, 2007, p. 121–138
11. Simó R, Hernández C. Intravitreous anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy. Diabetologia 2008;51:1574–1580
12. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26:859–870
13. Chun DW, Heier JS, Topping TM, Duker JS, Bankert JM. A pilot study of multiple

intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. Ophthalmology 2006;113:1706–1712
14. Nguyen QD, Shah SM, Heier JS, Do DV, Lim J, Boyer D, Abraham P, Campochiaro PA, READ-2 Study Group. Primary end point (six months) results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study. Ophthalmology 2009;116:2175–2181.e1
15. Cunningham ET Jr, Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, Goldbaum M, Guyer DR, Katz B, Patel M, Schwartz SD, Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112:1747–1757
16. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, Berrocal MH, Solis-Vivanco A, Farah ME. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. Ophthalmology 2007;114:743–750
17. Lam DS, Lai TY, Lee VY, Chan CK, Liu DT, Mohamed S, Li CL. Efficacy of 1.25 mg versus 2.5 mg intravitreal bevacizumab for diabetic macular edema: six-month results of a randomized controlled trial. Retina 2009;29:292–299
18. Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, Yaseri M, Ahmadieh H, Dehghan MH, Azarmina M, Moradian S, Peyman GA. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. Ophthalmology 2009;116:1142–1150
19. Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards AR, Beck RW, Bressler NM, Chan CK, Elman MJ, Friedman SM, Greven CM, Maturi RK, Pieramici DJ, Shami M, Singerman LJ, Stockdale CR. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. Ophthalmology 2007;114:1860–1867
20. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444
21. Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, Shams N. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–248
22. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431
23. Garcia-Arumi J. Safety profile of diabetic macular edema patients treated over 12 months with ranibizumab in the RESOLVE study. Poster presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology, 1–5 May 2010, Fort Lauderdale, FL
24. Lanzetta P, Burian G, Weichselberger A, Hashad Y. Safety profiles of diabetic versus non-diabetic AMD patients in randomized controlled clinical studies with ranibizumab. Poster presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology, 1–5 May 2010, Fort Lauderdale, FL
25. The Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064–1077.e35

Ranibizumab for Diabetic Macular Edema

Results from 2 Phase III Randomized Trials: RISE and RIDE

*Quan Dong Nguyen, MD, MSc,[1] David M. Brown, MD,[2] Dennis M. Marcus, MD,[3] David S. Boyer, MD,[4] Sunil Patel, MD, PhD,[5] Leonard Feiner, MD, PhD,[6] Andrea Gibson,[7] Judy Sy, PhD,[7] Amy Chen Rundle, MS,[7] J. Jill Hopkins, MD,[7] Roman G. Rubio, MD,[7] Jason S. Ehrlich, MD, PhD,[7] on behalf of the RISE and RIDE Research Group**

Purpose: To evaluate the efficacy and safety of intravitreal ranibizumab in diabetic macular edema (DME) patients.

Design: Two parallel, methodologically identical, phase III, multicenter, double-masked, sham injection–controlled, randomized studies.

Participants: Adults with vision loss from DME (best-corrected visual acuity [BCVA], 20/40–20/320 Snellen equivalent) and central subfield thickness ≥275 μm on time-domain optical coherence tomography (OCT).

Intervention: Monthly intravitreal ranibizumab (0.5 or 0.3 mg) or sham injections. Macular laser was available per-protocol–specified criteria.

Main Outcome Measures: Proportion of patients gaining ≥15 letters in BCVA from baseline at 24 months.

Results: In RISE (NCT00473330), 377 patients were randomized (127 to sham, 125 to 0.3 mg, 125 to 0.5 mg). At 24 months, 18.1% of sham patients gained ≥15 letters versus 44.8% of 0.3-mg ($P<0.0001$; difference vs sham adjusted for randomization stratification factors, 24.3%; 95% confidence interval [CI], 13.8–34.8) and 39.2% of 0.5-mg ranibizumab patients ($P<0.001$; adjusted difference, 20.9%; 95% CI, 10.7–31.1). In RIDE (NCT00473382), 382 patients were randomized (130 to sham, 125 to 0.3 mg, 127 to 0.5 mg). Significantly more ranibizumab-treated patients gained ≥15 letters: 12.3% of sham patients versus 33.6% of 0.3-mg patients ($P<0.0001$; adjusted difference, 20.8%; 95% CI, 11.4–30.2) and 45.7% of 0.5-mg ranibizumab patients ($P<0.0001$; adjusted difference, 33.3%; 95% CI, 23.8–42.8). Significant improvements in macular edema were noted on OCT, and retinopathy was less likely to worsen and more likely to improve in ranibizumab-treated patients. Ranibizumab-treated patients underwent significantly fewer macular laser procedures (mean of 1.8 and 1.6 laser procedures over 24 months in the sham groups vs 0.3–0.8 in ranibizumab groups). Ocular safety was consistent with prior ranibizumab studies; endophthalmitis occurred in 4 ranibizumab patients. The total incidence of deaths from vascular or unknown causes, nonfatal myocardial infarctions, and nonfatal cerebrovascular accidents, which are possible effects from systemic vascular endothelial growth factor inhibition, was 4.9% to 5.5% of sham patients and 2.4% to 8.8% of ranibizumab patients.

Conclusions: Ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME, with low rates of ocular and nonocular harm.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Ophthalmology 2012;119:789–801 © 2012 by the American Academy of Ophthalmology.

**Group members listed online (http://aaojournal.org).*

Diabetic retinopathy (DR), the most common microvascular complication of diabetes,[1] is the leading cause of new cases of vision loss and blindness among working-aged adults in the United States and most developed countries.[2,3] Diabetic macular edema (DME), swelling of the central retina that causes vision loss, is an advanced complication of DR[4]; the prevalence of DME increases from 0% to 3% in individuals with recent diagnoses of diabetes to 28% to 29% in those with diabetes for ≥20 years.[5] Because the population of people with diabetes is ~285 million worldwide[6] and growing rapidly, vision loss from DR is a significant public health issue, with considerable socioeconomic and quality-of-life impacts.[7]

In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular laser as standard care treatment by demonstrating that patients with clinically significant DME treated with laser experienced a 50% reduction in moderate vision loss over time compared with untreated patients.[8] However, in ETDRS and recent studies, relatively few patients with vision loss experienced significant improvements in best-corrected visual acuity (BCVA) after laser, and improvement

ISSN 0161-6420/12/$–see front matter
doi:10.1016/j.ophtha.2011.12.039

tended to occur slowly.[8–12] A treatment that rapidly and durably improves vision would be an important advance.

Diabetic macular edema results from pathologically increased retinal vascular permeability.[13] Recognition of vascular endothelial growth factor (VEGF) as the primary cytokine mediating this increase[14,15] and observation of increased intraocular VEGF levels in DME[16] led to the hypothesis that VEGF signaling blockade might be beneficial both in restoring normal retinal anatomy and reversing vision loss from macular edema. Ranibizumab is an anti-VEGF antibody fragment, designed for intraocular use, that neutralizes the biologic activity of all known active isoforms of VEGF.[17] Pilot studies demonstrated that intravitreal ranibizumab reduced macular edema and improved visual acuity (VA) in patients with DME.[18] Subsequent studies demonstrated that ranibizumab was superior to laser at 6 months and superior to both intravitreal steroids and laser at 12 months.[9,10,19,20] Herein, we report the results of two 24-month, phase III, randomized studies designed to evaluate long-term treatment with ranibizumab in patients with vision loss from DME.

Methods

Study Design

RISE (registered on ClinicalTrials.gov as NCT00473330) and RIDE (NCT00473382) are parallel phase III multicenter, double-masked, sham injection–controlled, randomized studies conducted at private and university-based retina specialty clinics in the United States and South America (65 principal investigators per study). One objective was to generate confirmatory evidence for regulatory purposes; thus, 2 identically designed studies were carried out. Two ranibizumab doses were chosen for regulatory purposes. Patients were recruited from June 2007 to January 2009, and the 24-month controlled treatment periods ended on November 16, 2010 (RISE), and January 12, 2011 (RIDE). The trials adhered to the tenets of the Declaration of Helsinki, were Health Insurance Portability and Accountability Act–compliant, and protocols were approved by institutional review boards, ethics committees, or as applicable. Patients provided written, informed consent.

Participants

One eye per patient was randomized. Eligible participants were aged ≥18 years with diabetes mellitus (type 1 or 2), decreased vision from DME (study eye BCVA, 20/40–20/320 Snellen equivalent using ETDRS testing), and macular edema (time-domain optical coherence tomography [OCT] central subfield thickness ≥ 275 μm). Key exclusion criteria were prior vitreoretinal surgery, or a recent history (within 3 months of screening) of panretinal or macular laser in the study eye, intraocular corticosteroids, or antiangiogenic drugs. Patients with uncontrolled hypertension, uncontrolled diabetes (glycosylated hemoglobin [HbA1c] > 12%), or recent (within 3 months) cerebrovascular accident (CVA), or myocardial infarction (MI) were excluded.

Randomization, Intervention, and Masking

Eligible patients were randomized[21] to monthly sham injections or intravitreal injections of 0.3 or 0.5 mg of ranibizumab. Beginning at month 3 all patients were evaluated monthly for the need for macular laser according to protocol-specified criteria: Central foveal thickness (CFT) ≥250 μm with a <50-μm change from the prior month, with no prior macular laser in the previous 3 months, and an assessment by the evaluating physician that macular laser

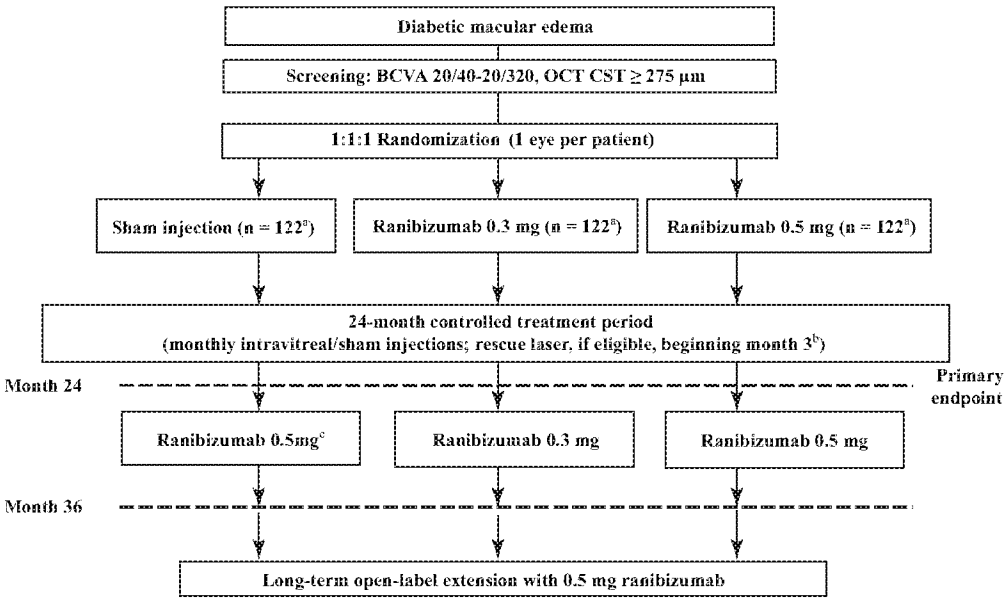


Figure 1. Study design. BCVA = best-corrected visual acuity; CST = central subfield thickness; OCT = optical coherence tomography. [a]Target enrollment, 122 patients per treatment group. [b]Starting at month 3, patients were evaluated monthly for rescue laser based on objective and subjective criteria as described in Methods. [c]After publication of a 12-month trial of ranibizumab, laser, and steroids for diabetic macular edema,[10] and consultation with the data monitoring committee, the studies were amended to allow early crossover (before month 25) to ranibizumab for patients receiving sham with persistent edema and vision loss. One patient in RISE and 3 patients in RIDE crossed over early (before month 25). These patients were analyzed in their original treatment groups per the intent-to-treat principle used for efficacy analyses.

would be beneficial. The goal of laser treatment was to apply photocoagulation in a grid pattern or directly to leaky microaneurysms in areas of retinal thickening and edema, avoiding treatment within the foveal avascular zone. Randomization was stratified by study eye BCVA (≤55 vs >55 ETDRS letters), baseline HbA1c (≤8% vs >8%), prior DME therapy in the study eye (yes vs no), and study site. Dynamic randomization was used to obtain approximately a 1:1:1 ratio among groups (Fig 1). Randomization was done via interactive phone system. The sponsor developed the specifications for the randomization, and a third party programmed and held the randomization algorithm. The studies were unmasked on February 10, 2011 (RISE), and March 22, 2011 (RIDE), when treatment assignments were made available to the study analysis team of the sponsor. Ocular assessments, including the need for macular laser, were made by evaluating ophthalmologists masked to patients' treatment assignments. Study treatments were administered by treating ophthalmologists unmasked to treatment assignments but masked to ranibizumab dose. To improve patient masking, all patients received subconjunctival anesthesia before sham or active injections (performed as previously described).[22] Study site personnel (except treating physicians and assistants), central reading center personnel, and the sponsor and its agents (except drug accountability monitors) were masked to treatment assignment. Treating physicians were masked to the assigned dose of ranibizumab. An independent statistical coordinating center performed the unmasked interim analyses for the data monitoring committee.

Assessments

Evaluations included vital signs, safety assessments, visual function questionnaires, and ocular assessments: BCVA measured with the ETDRS chart (4-m starting distance), contrast sensitivity, intraocular pressure, slit-lamp examination, indirect ophthalmoscopy, OCT, fluorescein angiography (FA), and fundus photography (FP). Study visits were scheduled every 30±7 days. The OCT, FA, and FP images were graded at a central reading center.

Outcomes

The primary efficacy measure was the proportion of patients gaining ≥15 ETDRS letters in BCVA score from baseline at 24 months (corresponding to 3 lines on the eye chart). Secondary outcomes at 24 months were mean change from baseline BCVA score over time, proportion of patients with BCVA Snellen equivalent of ≥20/40, mean change from baseline BCVA score over time in patients with focal edema as assessed on FA, proportion of patients losing <15 letters in BCVA score from baseline, mean change from baseline in OCT CFT over time, proportion of patients with a ≥3-step progression from baseline in ETDRS retinopathy severity on FP, proportion of patients with resolution of leakage on FA, and the mean number of macular laser treatments over time. Certain secondary endpoints were amended after the studies commenced but before unmasking study results, to be more consistent with literature and regulatory guidance received subsequent to initiation of the studies (Appendix 1; available at http://aaojournal.org).

Analysis

Efficacy Analyses. The sample size of 366 patients (122 per treatment group) per study provided 90% experiment-wise power to detect a statistically significant difference in the primary effi-

Table 1. Patient Demographic and Baseline Characteristics

Characteristic	RISE			RIDE		
		Ranibizumab			*Ranibizumab*	
	Sham (n = 127)	*0.3 mg (n = 125)*	*0.5 mg (n = 125)*	*Sham (n = 130)*	*0.3 mg (n = 125)*	*0.5 mg (n = 127)*
Mean age (SD), yrs*	61.8 (9.8)	61.7 (8.9)	62.8 (10.0)	63.5 (10.8)	62.7 (11.1)	61.8 (10.1)
Range, yrs	39–85	38–82	21–87	22–91	24–88	29–84
Male, n (%)	74 (58.3)	73 (58.4)	65 (52.0)	66 (50.8)	73 (58.4)	80 (63.0)
Race, n (%)†						
Asian	6 (4.7)	7 (5.6)	7 (5.6)	2 (1.5)	5 (4.0)	5 (3.9)
American Indian or Alaska Native	0	0	0	1 (0.8)	1 (0.8)	2 (1.6)
Black or African American	19 (15.0)	18 (14.4)	14 (11.2)	15 (11.5)	14 (11.2)	13 (10.2)
Native Hawaiian/other/Pacific Islander	1 (0.8)	2 (1.6)	1 (0.8)	0	1 (0.8)	0
White	101 (79.5)	97 (77.6)	97 (77.6)	104 (80.0)	99 (79.2)	105 (82.7)
Not available	0	1 (0.8)	6 (4.8)	8 (6.2)	5 (4.0)	2 (1.6)
Hispanic or Latino ethnicity, n (%)	24 (18.9)	20 (16.0)	25 (20.0)	37 (28.5)	33 (26.4)	31 (24.4)
Mean body mass index (SD)‡	31.4 (7.1)	32.3 (6.8)	32.9 (8.5)	32.3 (8.9)	32.3 (8.6)	31.3 (7.2)
Positive history of smoking, n (%)	60 (48.0)§	64 (51.2)	58 (46.4)	43 (33.6)‖	64 (51.6)‖	57 (45.6)‖
Mean duration of diabetes (SD), yrs*,¶	14.5 (9.9)	15.9 (9.9)	16.3 (8.5)	16.6 (10.6)	16.0 (9.8)	15.3 (10.1)
Mean HbA1c (SD), %**	7.7 (1.5)	7.7 (1.5)	7.7 (1.4)	7.6 (1.4)	7.6 (1.3)	7.6 (1.5)
≤8%, n (%)	80 (65.0)	81 (67.5)	82 (68.3)	84 (67.2)	79 (65.8)	83 (67.5)
>8%, n (%)	43 (35.0)	39 (32.5)	38 (31.7)	41 (32.8)	41 (34.2)	40 (32.5)

HbA1c = glycosylated hemoglobin; SD = standard deviation.
*At randomization.
†Patients who are of >1 race were counted for each category that they indicated.
‡Number of patients: 124, 122, and 124 (RISE) and 128, 125, and 126 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.
§Number of patients: 125.
‖Number of patients: 128, 124, and 125 in the sham, 0.3-mg, and 0.5-mg groups, respectively.
¶Number of patients: 123, 118, and 118 (RISE) and 122, 119, and 124 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.
**Number of patients: 123, 120, and 120 (RISE) and 125, 120, and 123 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.

Table 2. Study Eye Characteristics at Baseline

Characteristic	RISE			RIDE		
		Ranibizumab			Ranibizumab	
	Sham (n = 127)	0.3 mg (n = 125)	0.5 mg (n = 125)	Sham (n = 130)	0.3 mg (n = 125)	0.5 mg (n = 127)
Mean ETDRS letter score (SD)	57.2 (11.1)	54.7 (12.6)	56.9 (11.6)	57.3 (11.2)	57.5 (11.6)	56.9 (11.8)
Mean approximate Snellen equivalent	20/80+2	20/80	20/80+2	20/80+2	20/80+2	20/80+2
≤20/200, n (%)	10 (7.9)	17 (13.6)	10 (8.0)	10 (7.7)	9 (7.2)	11 (8.7)
>20/200 but <20/40, n (%)	92 (72.4)	91 (72.8)	91 (72.8)	95 (73.1)	92 (73.6)	91 (71.1)
≥20/40, n (%)	25 (19.7)	17 (13.6)	24 (19.2)	25 (19.2)	24 (19.2)	25 (19.7)
Mean CFT (SD), μm	467.3 (152.0)	474.5 (174.8)	463.8 (144.0)	447.4 (154.4)	482.6 (149.3)	463.8 (175.5)
Mean time from first known CSME diagnosis to randomization (SD), yrs*	2.3 (3.0)	2.1 (2.2)	2.1 (2.1)	2.4 (3.2)	1.6 (2.0)	1.9 (2.4)
Active or previously treated PDR present, n (%)†	34 (26.8)	28 (22.4)	32 (25.6)	28 (21.5)	31 (24.8)	34 (26.8)
Previous treatment for CSME, n (%)						
Any	94 (74.0)	94 (75.2)	102 (81.6)	92 (70.8)	86 (68.8)	88 (69.3)
Focal/grid laser	86 (67.7)	86 (68.8)	90 (72.0)	84 (64.6)	72 (57.6)	79 (62.2)
Steroids‡	35 (27.6)	39 (31.2)	50 (40.0)	36 (27.7)	32 (25.6)	37 (29.1)
Other	21 (16.5)	20 (16.0)	21 (16.8)	21 (16.2)	27 (21.6)	25 (19.7)

CFT = central foveal thickness; CSME = clinically significant macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; PDR = proliferative diabetic retinopathy; SD = standard deviation.
*Number of patients: 127, 124, and 123 in the sham, 0.3-mg, and 0.5-mg groups, respectively, in RISE and 126 in the 0.5-mg group in RIDE.
†Active PDR was a study enrollment exclusion criterion.
‡Intraocular or subtenon injection.

cacy measure between 1 or both ranibizumab groups and the control (expecting percentages of 35% for 0.5-mg ranibizumab-treated patients, 25% for 0.3-mg, and 13% for sham patients). The studies were not designed or powered to compare the 2 selected doses of ranibizumab, but rather to compare each ranibizumab dose against the sham comparator (2 doses were used for regulatory purposes). The intent-to-treat principle was used for efficacy analyses, with missing data imputed using the last observation carried forward method. To account for potential differences in baseline characteristics between treatment groups that may affect the outcome measures, efficacy analyses were stratified by the randomization stratification factors baseline BCVA (≤55, >55 letters), baseline HbA1c (≤8%, >8%), and prior therapy for DME (yes or no); reported differences and 95% confidence intervals were also adjusted for these baseline variables. For the primary endpoint and secondary efficacy endpoints based on binary variables, a comparison between each ranibizumab group and the control group was made using the Cochran-Mantel-Haenszel chi-square test stratified (adjusted) by the randomization stratification factors. For secondary efficacy endpoints that were continuous in nature (e.g., mean change from baseline in BCVA score), comparisons were made by fitting either an analysis of variance or analysis of covariance model, adjusting for the randomization stratification factors. For the secondary efficacy endpoint of mean

Table 4. Use of Macular and

Outcomes at Month 24	RISE		
		Ranibizumab	
	Sham (n = 127)	0.3 mg (n = 125)	0.5 mg (n = 125)
Number of macular focal/grid rescue laser treatments, mean (SD)	1.8 (1.8)	0.8 (1.2)	0.8 (1.3)
Difference vs sham (95% CI)†		−1.0 (−1.4 to −0.7)	−1.1 (−1.5 to −0.7)
Test for treatment difference vs sham‡		P<0.0001	P<0.0001
Median	1.0	0	0
Range	0–6	0–7	0–6
Received macular laser treatment, n (%; 95% CI)	94 (74.0; 66.4–81.6)	49 (39.2; 30.6–47.8)	44 (35.2; 26.8–43.6)
Difference vs sham (95% CI)†		−35.0 (−46.4 to −23.7%)	−39.3 (−50.7 to −28.0)
Test for treatment difference vs sham§		P<0.0001	P<0.0001
Proportion of patients who received PRP laser, n (%)‖	14 (11.0)	0	1 (0.8)

CI = confidence interval; PRP = panretinal photocoagulation; SD = standard deviation.
The last-observation-carried-forward method was used to impute missing data. The mean number of macular lasers is reported with no imputation.
*Starting at month 3, patients were evaluated monthly for macular focal/grid laser based on the objective and subjective criteria as described in the
†Difference is adjusted for baseline visual acuity (≤55, >55 Early Treatment Diabetic Retinopathy Study [ETDRS] letters), baseline glycosylated
‡Wilcoxon test stratified by baseline visual acuity (≤55, >55 ETDRS letters), baseline HbA1c (≤8%, >8%), and prior treatment for diabetic macular
§Cochran-Mantel-Haenszel χ^2 (stratified by baseline visual acuity [≤55, >55 ETDRS letters], baseline HbA1c [≤8%, >8%], and prior treatment for
‖Not a prespecified endpoint; no statistical testing performed. Data are reported in context of safety outcomes and laser treatments performed for diabetic

change from baseline in CFT over time up to 24 months, the respective baseline CFT value was included as a continuous variable (covariate) in the analysis of covariance model. The mean number of macular laser treatments during 24 months was compared between each ranibizumab group and sham using a stratified Wilcoxon test. Additional details are in the supplemental material (Appendix 1; available at http://aaojournal.org).

Safety Analyses. Safety was assessed through collection and summary of ocular and nonocular adverse events (AEs), serious AEs (SAEs), ocular assessments, deaths, laboratory results, vital signs, and antibodies to ranibizumab. At each study visit, nondirective questioning was used to elicit AE reports from patients. All AEs and SAEs, whether volunteered by the patient, discovered by study site personnel during questioning, or detected by examination, laboratory testing, or other means, were recorded in the patient record and case report forms. Safety analyses included all patients receiving ≥1 ranibizumab or sham injection. Patients were analyzed according to actual treatment received before optional crossover for patients randomized to the sham group.

All data analyses occurred after all patients completed the month 24 visit or discontinued early. A Data Monitoring Committee (3 ophthalmologists and 1 biostatistician) was established to monitor safety and study conduct by periodically reviewing unmasked data. Each interim safety analysis was allocated a type I error $\alpha = 0.0001$ to account for review of VA data forming the basis of the primary efficacy endpoint.

Results

In total, 759 patients were enrolled and randomized to study treatment (377 in RISE and 382 in RIDE; Fig 2, available at http://aaojournal.org). Randomized groups were generally well-balanced for baseline demographic (Table 1) and study eye characteristics, including history of prior treatment (Table 2); however, in RISE, more patients in the 0.3-mg ranibizumab group had a BCVA <20/200, and more patients in the 0.5-mg ranibizumab group in both studies had previously received intraocular or periocular steroids for DME. The 2-year study period was completed by 83.3% of patients in RISE and by 84.6% in RIDE. The median number of ranibizumab injections was 24 (Table 3, available at http://aaojournal.org). The mean number of macular laser treatments over 24 months was 1.8 and 1.6 in the sham groups and 0.3 to 0.8 in the ranibizumab groups (Table 4). Substantially more sham-treated patients received macular laser under the protocol-specified criteria or underwent panretinal photocoagulation for proliferative DR (PDR; Table 4).

Visual Acuity Outcomes

In both studies, statistically significantly greater numbers of patients randomized to ranibizumab gained ≥15 ETDRS letters from baseline at 24 months. In RISE, 44.8% of patients receiving 0.3 mg ranibizumab and 39.2% of patients receiving 0.5 mg ranibizumab gained ≥15 letters compared with 18.1% of sham-treated patients (Table 5, available at http://aaojournal.org; Fig 3). In RIDE, corresponding proportions were 33.6%, 45.7%, and 12.3%, respectively (Table 5; Fig 3). Ranibizumab treatment led to rapid vision improvements, with statistically significant changes versus sham observed as early as 7 days after the first injection (Fig 4). Mean BCVA in ranibizumab groups continued to improve steadily, with patients experiencing an average benefit over sham (adjusted for baseline variables) of 8.5 to 9.9 ETDRS letters at month 24 (Table 5; Fig 4). Fewer ranibizumab-treated patients experienced significant (≥15 ETDRS letters) vision loss (Tables 5 and 6; Fig 3 and Fig 5 [available at http://aaojournal.org]). More patients in the ranibizumab groups achieved Snellen BCVA of ≥20/40 at month 24 compared with sham ($P<0.0001$ for each ranibizumab group vs sham; Table 5; Fig 3).

The effects of demographic and baseline ocular characteristics on efficacy outcomes were examined in prespecified subgroup analyses. As expected, baseline BCVA impacted efficacy[23]; patients with worse baseline BCVA experienced greater improvements, and patients with better baseline BCVA (and less ability to gain letters) experienced lesser improvements (Table 7, available at http://aaojournal.org). No prespecified subgroup was identified

Panretinal Photocoagulation*

RIDE		
	Ranibizumab	
Sham (*n* = 130)	*0.3 mg* (*n* = 125)	*0.5 mg* (*n* = 127)
1.6 (1.6)	0.7 (1.4)	0.3 (0.7)
	−0.9 (−1.3 to −0.5)	−1.3 (−1.6 to −1.0)
	P<0.0001	*P*<0.0001
1.0	0	0
0–7	0–7	0–5
91 (70.0; 62.1–77.9)	45 (36.0; 27.6–44.4)	25 (19.7; 12.8–26.6)
	−32.8 (−44.2 to −21.4)	−49.8 (−60.1 to −39.6)
	P<0.0001	*P*<0.0001
16 (12.3)	2 (1.6)	2 (1.6)

methods. Panretinal laser was available as clinically indicated.
hemoglobin (HbA1c; ≤8%, >8%), and prior treatment for DME (yes, no).
edema (DME; yes, no).
DME [yes, no]).
retinopathy during these studies.

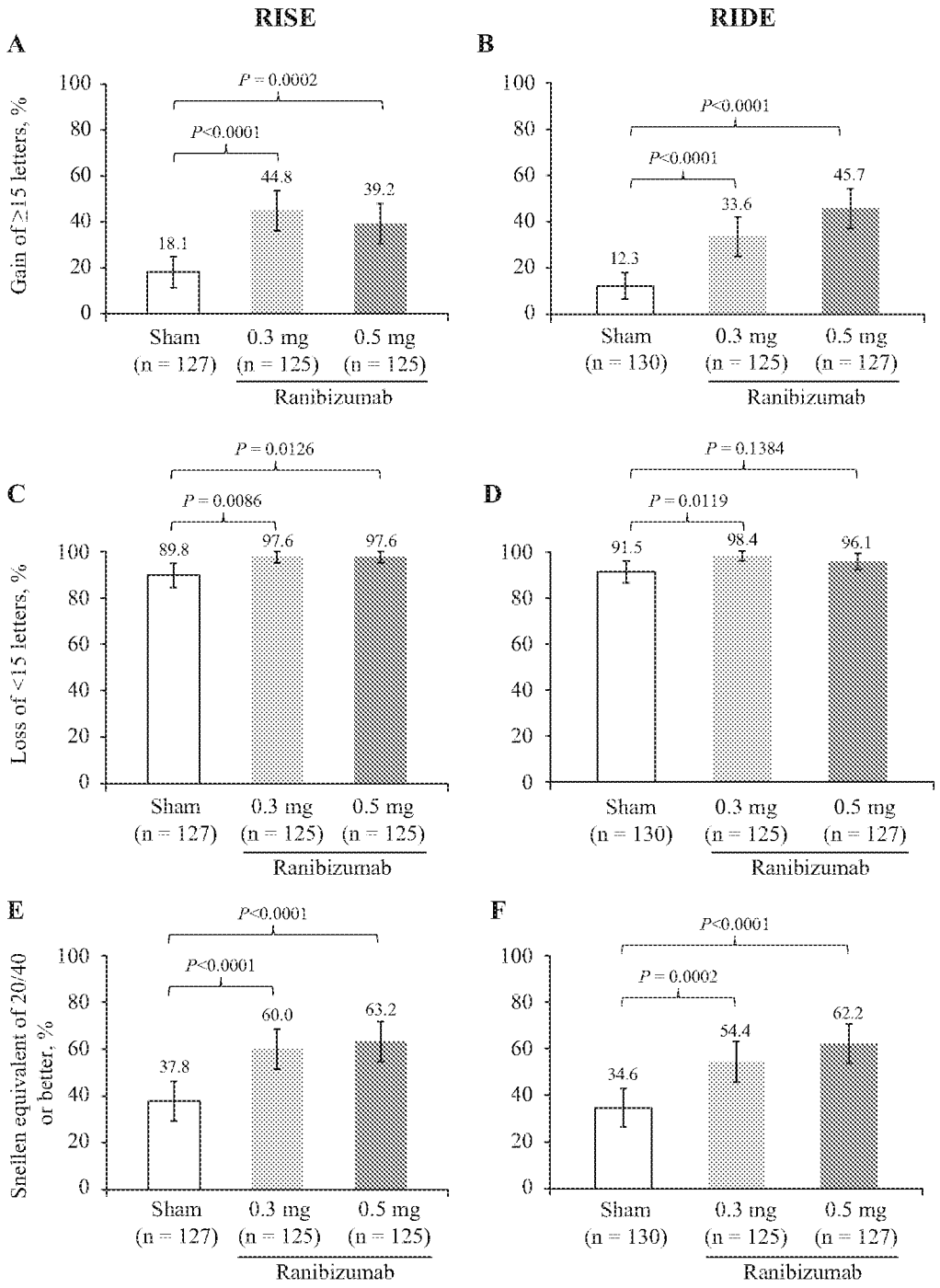


Figure 3. Visual acuity outcomes at 24 months. Primary efficacy endpoint: percentage of patients who gained ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline at 24 months in RISE (**A**) and in RIDE (**B**). Secondary efficacy endpoints were (i) percentage of patients who lost <15 ETDRS letters from baseline visual acuity at 24 months in RISE (**C**) and in RIDE (**D**); and (ii) percentage of patients with vision of the Snellen equivalent of ≥20/40 in RISE (**E**) and in RIDE (**F**). The proportions of patients with baseline Snellen equivalent of ≥20/40 are in Table 2, Vertical bars are 95% confidence intervals (CIs) for the percentage. Outcomes on bar charts are unadjusted. *P* values (treatment comparisons) are based on the Cochran-Mantel-Haenszel chi-square test stratified according to the baseline visual acuity (≤55, >55 letters), baseline glycosylated hemoglobin (≤8%, >8%), and prior treatment for diabetic macular edema (yes, no). See Table 5 for 95% CIs for the differences.

in which sham patients experienced better visual outcomes. Patients with predominantly focal DME on angiography had mean BCVA improvements at month 24 similar to the overall population (Table 5).

Anatomic Outcomes

Improvements in VA among ranibizumab-treated patients were paralleled by rapid reductions in macular edema measured with

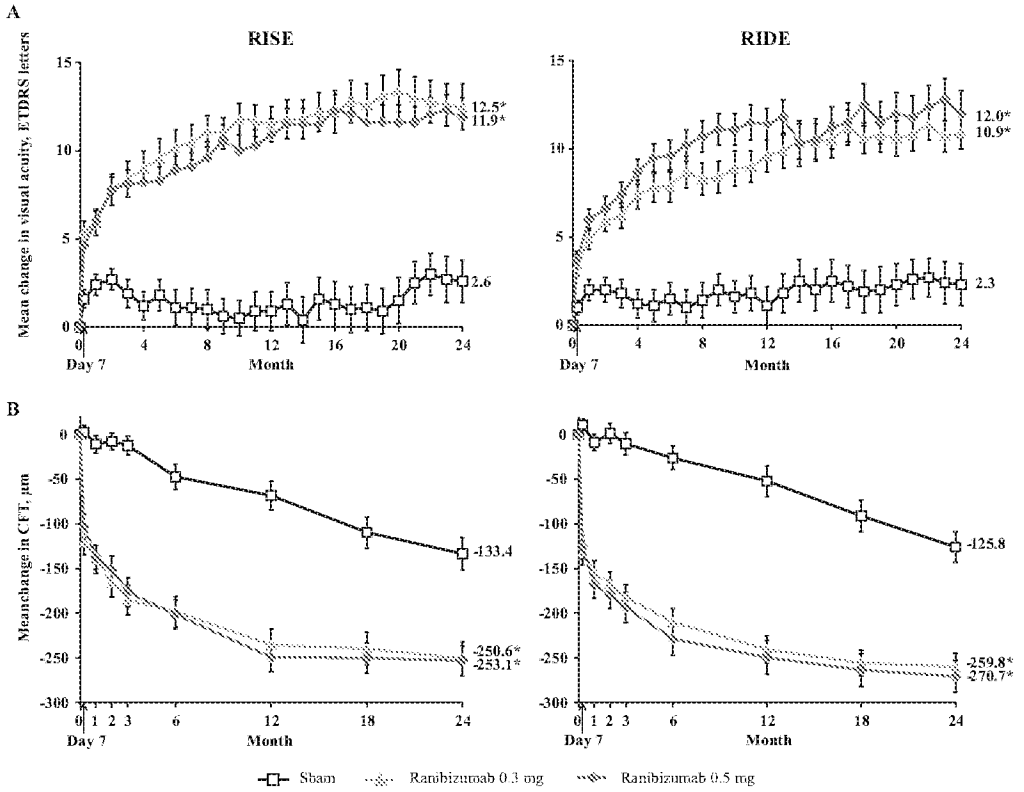


Figure 4. Changes in (A) visual acuity and (B) central foveal thickness (CFT) from baseline through 24 months. Number of patients: 127, 125, and 125 (RISE) and 130, 125, and 127 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward imputation method was used. *$P<0.0001$ versus sham (analysis of variance t test [stratified]). Differences were statistically significant starting at the first posttreatment observation (day 7) and at each point thereafter; a hierarchical testing strategy controlled for multiple comparisons. ETDRS = Early Treatment Diabetic Retinopathy Study.

OCT (Fig 4). Differences between ranibizumab and sham groups were statistically significant at day 7 (first posttreatment measurement) and at each point thereafter. Resolution of leakage on FA and of macular edema on OCT both were statistically significantly more common among ranibizumab-treated patients (Table 5; Fig 6).

Patients randomized to ranibizumab were less likely to develop PDR (Table 8, available at http://aaojournal.org; Fig 6). Notably, we observed lower rates of retinopathy progression and higher rates of retinopathy improvement in ranibizumab-treated eyes, measured by the ETDRS retinopathy severity scale (Table 8).

Ocular Harm

Serious AEs affecting study eyes are summarized in Table 9. Overall, the most common SAE was vitreous hemorrhage, which occurred in 4 sham-treated and 2 ranibizumab-treated eyes in RISE and in 3 sham-treated eyes in RIDE. Serious intraocular inflammation was uncommon among ranibizumab-treated patients, occurring only once. Serious AEs arising from the injection procedure were also uncommon; 1 case of endophthalmitis occurred in RISE and 3 in RIDE, along with 3 cases of traumatic cataract and 1 rhegmatogenous retinal detachment out of 10 584 intravitreal injections (Table 10, available at http://aaojournal.org).

Ocular AEs in the study eye are summarized in Table 11 (available at http://aaojournal.org). Most were reported as mild or moderate. Rates of cataract, intraocular inflammation, and glaucoma AEs were similar among the sham and ranibizumab groups. Increased intraocular pressure after the injection was more likely in ranibizumab-treated patients, as expected, because sham-treated patients did not receive actual injections. In ranibizumab-treated patients, AEs related to worsening of DR, such as retinal neovascularization and vitreous hemorrhage, were less common. Three traction retinal detachments occurred in sham-treated patients.

Systemic Harm

Systemic safety was ascertained through analysis of overall systemic AEs and events potentially related to systemic VEGF inhibition. The most frequent systemic SAEs were those common to patients with advanced diabetes, such as MI, pneumonia, and congestive heart failure, with similar rates across treatment groups (Table 12, available at http://aaojournal.org). Analysis of arterial thromboembolic events, a subgroup of events potentially related to systemic VEGF inhibition, can be challenging because of variations in the definition, assessment, and reporting of events. Antiplatelet Trialists' Collaboration (APTC) criteria mitigate some of these issues by focusing on a more restricted but well-defined spectrum of SAEs: Vascular deaths, deaths of unknown cause, nonfatal MIs, and nonfatal cerebrovascular accidents (CVAs).[24] Systemic SAEs potentially related to VEGF inhibition and categorized by APTC definitions are summarized in Table 13. Among APTC SAEs, deaths of vascular or unknown cause and CVAs were slightly more common in patients treated with ranibizumab. Overall, SAEs potentially related to systemic VEGF inhibition occurred

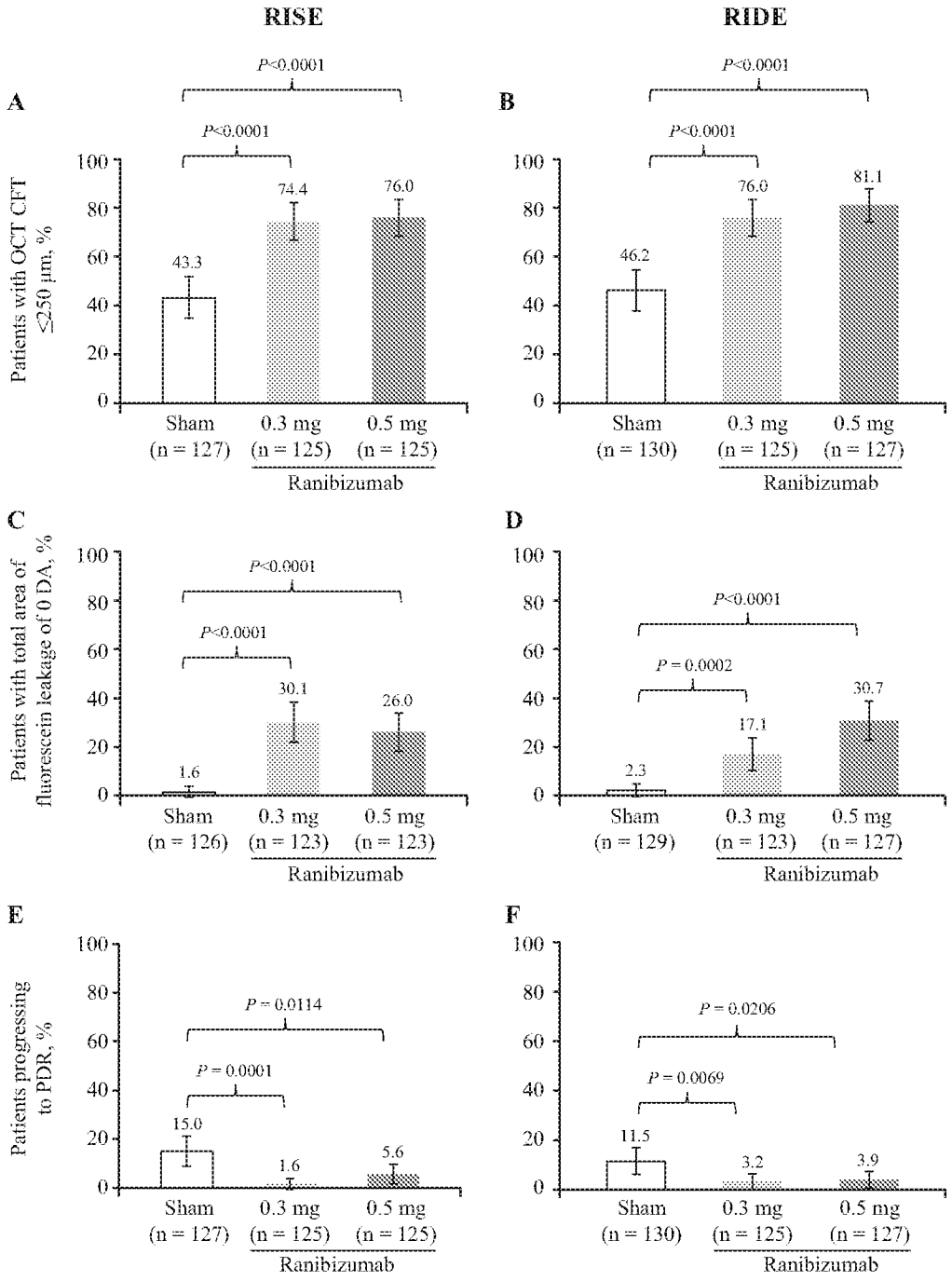


Figure 6. Exploratory analysis: proportion of patients without residual edema in (**A**) RISE and in (**B**) RIDE; secondary outcome measure: proportion of patients with resolution of leakage in (**C**) RISE and in (**D**) RIDE; proportion of patients progressing to proliferative diabetic retinopathy (PDR) in (**E**) RISE and in (**F**) RIDE. A patient was considered to have progressed to PDR by month 24 if, for any of these conditions, neovascularization was not present at baseline and was present at any postbaseline visit at or before month 24: neovascularization on the optic disc, elsewhere on the retina, or on the iris. Vertical bars are 95% confidence interval (CIs) for the percentages. Outcomes on bar charts are unadjusted. *P* values (treatment comparisons) are based on the Cochran-Mantel-Haenszel chi-square test stratified according to the baseline visual acuity (≤55, >55 letters), baseline glycosylated hemoglobin (≤8%, >8%), and prior treatment for diabetic macular edema (yes, no). See Table 5 for 95% CIs for the differences. CFT = central foveal thickness; DA = disc area; OCT = optical coherence tomography.

in 10.6% and 9.4% of sham-treated patients in RISE and RIDE, respectively, and in 5.6% to 11.9% of ranibizumab-treated patients across the studies. The APTC events occurred in 4.9% and 5.5% of sham-treated and 2.4% to 8.8% of ranibizumab-treated patients (Table 13).

Discussion

The RISE and RIDE studies demonstrate that ranibizumab significantly reverses vision loss from DME, and, impor-

Table 9. Study Eye Serious Adverse Events (SAEs) Through Month 24

SAEs, n (%) MedDRA Preferred Term	RISE			RIDE		
		Ranibizumab			*Ranibizumab*	
	Sham (n = 123)	*0.3 mg (n = 125)*	*0.5 mg (n = 126)*	*Sham (n = 127)*	*0.3 mg (n = 125)*	*0.5 mg (n = 124)*
Any SAE	9 (7.3)	4 (3.2)	7 (5.6)	7 (5.5)	4 (3.2)	12 (9.7)
Angle closure glaucoma	0	0	0	0	0	1 (0.8)
Cataract	0	0	0	0	1 (0.8)	2 (1.6)
Cataract traumatic	0	1 (0.8)	1 (0.8)	0	0	1 (0.8)
Choroidal neovascularization	1 (0.8)	0	0	0	0	0
Corneal abrasion	0	0	0	0	0	1 (0.8)
Corneal opacity	0	0	0	0	0	1 (0.8)
Diabetic retinal edema	0	1 (0.8)	0	0	0	0
Drug administration error	0	0	0	1 (0.8)	0	0
Endophthalmitis	0	1 (0.8)	0	0	1 (0.8)	2 (1.6)
Intraocular pressure increased	0	0	0	0	0	1 (0.8)
Macular edema	2 (1.6)	0	0	0	0	0
Medication error	0	1 (0.8)	2 (1.6)	0	1 (0.8)	0
Posterior capsule opacification	1 (0.8)	0	0	0	0	0
Retinal detachment	1 (0.8)*	0	0	0	0	1 (0.8)
Retinal hemorrhage	0	0	1 (0.8)	1 (0.8)	0	0
Retinal tear	0	0	1 (0.8)	0	0	0
Uveitis	0	0	0	0	1 (0.8)	0
Visual acuity reduced†	2 (1.6)	0	1 (0.8)	2 (1.6)	0	2 (1.6)
Vitreous hemorrhage	4 (3.3)	0	2 (1.6)	3 (2.4)	0	0

MedDRA = Medical Dictionary for Regulatory Activities, Version 13.1.
*Traction retinal detachment.
†Causes a decrease of ≥30 letters in visual acuity (VA; compared with the last assessment of VA before the most recent treatment) lasting more than 1 hour.

tantly, provides the longest term controlled evidence to date. Benefits of ranibizumab were observed as early as 7 days after treatment initiation, and initial improvements were maintained and subsequently built upon. Across all measures of vision improvement, monthly ranibizumab therapy was superior to sham; in addition to the primary efficacy outcome (a gain of ≥15 letters or 3 eye chart lines), a nearly 2-line benefit over sham was observed for average vision change, and more ranibizumab-treated patients had Snellen equivalent BCVA of ≥20/40 at month 24. This level of acuity is important for key vision-related tasks, such as driving and reading. Results of these studies were consistent across a variety of patients and DME subtypes: Outcomes were superior to sham in all prespecified subgroups, including treatment-naïve and previously treated patients, and patients with focal (but foveal-involving) edema. Pharmacodynamic benefits on retinal thickness were consistent with visual outcomes.

Patients with DR lose vision not only from DME, but also from complications of PDR, such as vitreous hemorrhage. Notably, patients treated with ranibizumab experienced fewer such events, and fewer developed PDR or underwent panretinal photocoagulation. Although few patients lost ≥15 ETDRS letters, a significant difference over sham was observed in both ranibizumab groups in RISE and in the 0.3-mg group in RIDE; the 0.5-mg group in RIDE trended similarly. Many more eyes treated with ranibizumab showed substantial (≥2- and ≥3-step) improvements in retinopathy severity on FP using the ETDRS Retinopathy Severity Scale for Eyes, and fewer showed substantial worsening. The clinical significance of retinopathy improvement on the ETDRS scale remains unclear, but retinopathy worsening is clearly associated with adverse visual outcomes, and management of PDR with either vitrectomy or panretinal photocoagulation carries substantial morbidity. Panretinal photocoagulation destroys retina and may result in reduced visual field and poor central vision.[25] Avoidance of these procedures is an additional and important potential benefit. Whether and for how long the beneficial effects of ranibizumab on retinopathy severity and progression persist after therapy cessation, however, also needs to be determined; a small study demonstrated recurrence of disease after pegaptanib treatment cessation in PDR patients. The current studies were not designed to address this question.

The beneficial effects of ranibizumab observed in these studies must be balanced against potential harms. Ocular safety was consistent with prior large studies of ranibizumab. Even in patients with diabetes, who are susceptible to infection, endophthalmitis rates (4/10; 584 injections) were similar to those in other large non-DME series, but because patients require multiple injections, physicians should apply best practices for infection control. From a systemic perspective, DME is a sign of end-organ microvascular damage. Use of VEGF antagonists may be of concern because patients with DME are at elevated risk for MI and CVA compared with patients with diabetes without ophthalmic complications (Pharmacoepidemiol Drug Saf 18

Table 13. Serious Adverse Events (SAEs) Potentially Related to Systemic Inhibition of Vascular Endothelial Growth Factor A, and Antiplatelet Trialists' Collaboration (APTC) Events (MI, CVAs, and Deaths) through Month 24

	RISE			RIDE		
		Ranibizumab			Ranibizumab	
SAE, n (%) MedDRA Preferred Term	Sham (n = 123)	0.3 mg (n = 125)	0.5 mg (n = 126)	Sham (n = 127)	0.3 mg (n = 125)	0.5 mg (n = 124)
Any SAE	13 (10.6)	7 (5.6)	15 (11.9)	12 (9.4)	12 (9.6)	7 (5.6)
Acute MI	0	0	3 (2.4)	0	4 (3.2)	0
MI	3 (2.4)	2 (1.6)	1 (0.8)	6 (4.7)	4 (3.2)	3 (2.4)
Angina pectoris	1 (0.8)	0	1 (0.8)	0	0	0
Angina unstable	0	0	0	2 (1.6)	0	0
CVA‡	1 (0.8)	1 (0.8)	4 (3.2)	2 (1.6)	2 (1.6)	3 (2.4)
Ischemic stroke	1 (0.8)	0	0	0	0	0
Lacunar infarction	0	0	1 (0.8)	0	0	0
Transient ischemic attack	3 (2.4)	0	1 (0.8)	2 (1.6)	1 (0.8)	0
Femoral artery occlusion	0	1 (0.8)	0	0	0	1 (0.8)
Hypertension	1 (0.8)	1 (0.8)	4 (3.2)	0	2 (1.6)	2 (1.6)
Duodenal ulcer hemorrhage	1 (0.8)	0	0	0	0	0
Peptic ulcer hemorrhage	0	0	0	0	1 (0.8)	0
Gastrointestinal hemorrhage	0	0	1 (0.8)	2 (1.6)	0	0
Hematuria	1 (0.8)	0	0	0	0	0
Lower gastrointestinal hemorrhage	0	0	1 (0.8)	0	0	0
Rectal hemorrhage	0	1 (0.8)	0	0	0	0
Retroperitoneal hemorrhage	1 (0.8)	0	0	0	0	0
Diabetic nephropathy	1 (0.8)	0	0	0	1 (0.8)	0
Nephrotic syndrome	0	0	1 (0.8)	0	0	0
Colitis ischemic	0	2 (1.6)	1 (0.8)	0	0	0
Large intestine perforation	0	0	1 (0.8)	0	0	0
Total APTC events*	6 (4.9)	3 (2.4)	11 (8.7)§	7 (5.5)	11 (8.8)	7 (5.6)
Deaths, overall	1 (0.8)	3 (2.4)	5 (4.0)	2 (1.6)	4 (3.2)	6 (4.8)
Vascular death	1 (0.8)	1 (0.8)	3 (2.4)	2 (1.6)	4 (3.2)	3 (2.4)
Nonvascular death	0	2 (1.6)	1 (0.8)	0	0	3 (2.4)
Unknown cause	0	0	1 (0.8)§	0	0	0
MI or CVA, overall	5 (4.1)	3 (2.4)	9 (7.1)	7 (5.5)	9 (7.2)	5 (4.0)
MI, overall	3 (2.4)	2 (1.6)	4 (3.2)	6 (4.7)	7 (5.6)	3 (2.4)
Nonfatal MI	3 (2.4)	1 (0.8)	4 (3.2)	4 (3.1)	6 (4.8)	2 (1.6)
Fatal MI†	0	1 (0.8)	0	2 (1.6)	1 (0.8)	1 (0.8)
CVA, overall	2 (1.6)	1 (0.8)	5 (4.0)	2 (1.6)	2 (1.6)	3 (2.4)
Nonfatal CVA	2 (1.6)	1 (0.8)	3 (2.4)	1 (0.8)	1 (0.8)	2 (1.6)
Fatal CVA	0	0	2 (1.6)§	1 (0.8)	1 (0.8)	1 (0.8)

CVA = cerebrovascular accident; MedDRA = Medical Dictionary for Regulatory Activities, Version 13.1; MI = myocardial infarction.
*Includes vascular deaths, deaths of unknown cause, nonfatal MIs, and nonfatal CVAs.
†Fatal means the patient did not survive to the end of the 24-month controlled treatment period, not that the MI or CVA was the proximate cause of death.[24]
‡CVA includes the MedDRA Preferred Terms of "cerebrovascular accident," "lacunar infarction," and "ischemic stroke," which were the event terms that occurred during the 24-month treatment periods in RIDE and RISE.
§Note. The 0.5-mg ranibizumab group includes 1 patient randomized to sham and who received sham, had a stroke (in 2008), received a single dose of 0.5-mg ranibizumab in error (2009), and died of unknown cause (2010). This patient was assigned to 0.5-mg group for all safety analyses per the prespecified safety analysis population criteria, as defined in Appendix 1.

[suppl 1]:S52, 2009).[26] In RISE and RIDE, the incidence of APTC-type events and those related to systemic VEGF inhibition were overall similar among sham and ranibizumab groups. Although deaths and CVAs were numerically higher in ranibizumab groups (CVAs, 1.6% of sham and 0.8%–4.0% of ranibizumab patients; deaths, 0.8% and 1.6% of sham and 2.4%–4.8% of ranibizumab-treated patients), this has not been observed in related studies. The Diabetic Retinopathy Clinical Research Network Protocol I showed results opposite to those observed in RISE and RIDE—higher rates of vascular death, MI, and cerebrovascular accident were seen in sham-treated patients (vs ranibizumab), with a patient cohort similar to RISE and RIDE,[11] and RESTORE showed balanced, low rates among laser and ranibizumab groups.[9] Additional follow-up of patients in these studies will provide further long-term guidance on systemic safety.

Certain limitations exist in RISE and RIDE. Selection bias is always a concern in considering the real-world application of clinical trial data; patients in RISE and RIDE may have had more severe or treatment-refractory disease that led physicians and patients to consider enrollment in the studies. The prespecified subgroup analyses demonstrating similar benefits of ranibizumab regardless of history of prior

DME therapy somewhat mitigates this concern. In addition, ranibizumab was not compared directly with macular laser for several reasons, including the difficulty in adequately masking laser treatment; instead, both ranibizumab and sham groups were able to receive rescue laser based on anatomic criteria and investigator discretion. The mean number of laser treatments in the sham groups was 1.8 (RISE) and 1.6 (RIDE), which some may consider insufficient over 2 years; however, the majority of eyes had undergone ≥1 macular laser treatment before enrollment and may have had DME in locations not amenable to further laser treatment, thus prompting recruitment into the studies. Moreover, although the investigator discretion allowed in the protocol-specified laser criteria may have potentially introduced bias toward undertreatment with laser, the visual and anatomic outcomes in the sham groups were similar to those observed in laser groups in several recent DME studies, irrespective of the number of laser treatments applied.[9,10,27] Thus, the BCVA outcomes in the RISE and RIDE sham groups likely represent an appropriate benchmark for comparing the additional benefits of ranibizumab in DME. Finally, RISE and RIDE evaluated a rigorous monthly treatment regimen, which may generate the best outcomes based on known pharmacokinetics but may not be practical for all patients. Data from the RESTORE and DRCR.net Protocol I studies provide guidance on more flexible or individualized ranibizumab dosing regimens for DME that were not evaluated in RISE and RIDE.[9,10]

The results of RISE and RIDE should be interpreted in the context of other trials. The ETDRS established focal laser as the mainstay of DME treatment in preventing VA loss.[8] After reports that intravitreal triamcinolone demonstrated short-term benefits, many clinicians favored steroids over laser for DME.[12,28] However, when triamcinolone was evaluated against laser in a randomized trial, steroids were inferior at 2 years with substantially higher rates of complications, surgical interventions, and 3-line vision loss.[12] A recent study demonstrated visual benefits over sham with an extended-release steroid-eluting implant,[27] but the magnitude of vision improvement was substantially lower than that observed with ranibizumab, with high rates of cataract surgery and elevated intraocular pressure. Studies of other VEGF antagonists (e.g., bevacizumab and pegaptanib) demonstrate evidence of clinical activity in DME. Although the extent of improvements over control seen with ranibizumab were not observed in those studies for either visual or anatomic endpoints, it is difficult to draw conclusions from smaller, shorter studies.[29–31] Finally, although RISE and RIDE did not directly compare ranibizumab with laser, this was accomplished in two 12-month controlled studies,[9,10] which demonstrated that ranibizumab (with prompt or deferred laser, or as monotherapy without laser) is superior to laser alone with respect to VA outcomes over ≤2 years.

For physicians managing diabetes and from a public health perspective, these data should be discussed with patients to underscore the importance of appropriate eye care to address the challenge of vision loss. Compliance with established screening guidelines is poor; only 40% to 50% of US adults with diabetes receive recommended eye examinations.[32] Ophthalmologists now have a substantial body of evidence supporting ranibizumab treatment as a new approach to DME management, focusing not only on vision preservation, but also on vision improvement. Treatment with ranibizumab also has beneficial effects on retinopathy progression and risk of further vision loss, and tolerable risks of harm. The present studies of ranibizumab provide the longest term evidence to date that visual loss from DME can be reversed, and clinically significant, sustained visual improvements can be achieved.

References

1. Fong DS, Aiello LP, Ferris FL III, Klein R. Diabetic retinopathy. Diabetes Care 2004;27:2540–53.
2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2011. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011:8. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed April 20, 2011.
3. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005–2008. JAMA 2010; 304:649–56.
4. Johnson MW. Etiology and treatment of macular edema. Am J Ophthalmol 2009;147:11–21.
5. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464–74.
6. International Diabetes Federation. IDF Diabetes Atlas, 4th ed. Brussels, Belgium: IDF Executive Office; 2009. Available at: http://www.diabetesatlas.org/. Accessed April 20, 2011.
7. Javitt JC, Aiello LP, Chiang Y, et al. Preventive eye care in people with diabetes is cost-saving to the federal government: implications for health-care reform. Diabetes Care 1994;17: 909–17.
8. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–806.
9. Mitchell P, Bandello F, Schmidt-Erfurth U, et al, RESTORE Study Group. The RESTORE Study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615–25.
10. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064–77.
11. Diabetic Retinopathy Clinical Research Network Writing Committee, Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118:609–14.
12. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115:1447–59.
13. Cunha-Vaz J, Faria de Abreu JR, Campos AJ. Early breakdown of the blood-retinal barrier in diabetes. Br J Ophthalmol 1975;59:649–56.
14. Qaum T, Xu Q, Joussen AM, et al. VEGF-initiated blood-retinal barrier breakdown in early diabetes. Invest Ophthalmol Vis Sci 2001;42:2408–13.

15. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. Ophthalmology 1996;103:1820–8.
16. Funatsu H, Yamashita H, Noma H, et al. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. Am J Ophthalmol 2002;133:70–7.
17. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26:859–70.
18. Nguyen QD, Tatlipinar S, Shah SM, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. Am J Ophthalmol 2006;142:961–9.
19. Nguyen QD, Shah SM, Heier JS, et al, READ-2 Study Group. Primary end point (six months) results of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) study. Ophthalmology 2009;116:2175–81.
20. Nguyen QD, Shah SM, Khwaja AA, et al, READ-2 Study Group. Two-year outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) study. Ophthalmology 2010;117:2146–51.
21. Signorini DF, Leung O, Simes RJ, et al. Dynamic balanced randomization for clinical trials. Stat Med 1993;12:2343–50.
22. Brown DM, Campochiaro PA, Singh RP, et al, CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010;117:1124–33.
23. Beck RW, Maguire MG, Bressler NM, et al. Visual acuity as an outcome measure in clinical trials of retinal diseases. Ophthalmology 2007;114:1804–9.
24. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81–106.
25. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology 1991;98(suppl):766–85.
26. Hirai FE, Knudtson MD, Klein BE, Klein R. Clinically significant macular edema and survival in type 1 and type 2 diabetes. Am J Ophthalmol 2008;145:700–6.
27. Campochiaro PA, Brown DM, Pearson A, et al, FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology 2011;118:626–35.
28. Martidis A, Duker JS, Greenberg PB, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002;109:920–7.
29. Phase 3 study showed MACUGEN improved vision over standard of care in patients with diabetic macular edema [press release]. New York: Pfizer Inc; June 5, 2010. Available at: http://media.pfizer.com/files/news/press_releases/2010/pfizer_macugen_dme_060510.pdf. Accessed April 20, 2011.
30. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal *B*evacizumab *or L*aser *T*herapy in the management of diabetic macular edema (BOLT study): 12-month data: report 2. Ophthalmology 2010;117:1078–86.
31. Diabetic Retinopathy Clinical Research Network. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. Ophthalmology 2007;114:1860–7.
32. Bragge P, Gruen RL, Chau M, et al. Screening for presence or absence of diabetic retinopathy: a meta-analysis. Arch Ophthalmol 2011;129:435–44.

Footnotes and Financial Disclosures

Originally received: August 28, 2011.
Final revision: December 6, 2011.
Accepted: December 21, 2011.
Available online: February 11, 2012. Manuscript no. 2011-1287.

[1] Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.

[2] Retina Consultants of Houston, The Methodist Hospital, Houston, Texas.

[3] Southeast Retina Center, Augusta, Georgia.

[4] Retina Vitreous Associates Medical Group, Los Angeles, California.

[5] West Texas Retina, Abilene, Texas.

[6] Retina Associates of New Jersey, Teaneck, New Jersey.

[7] Genentech, Inc., South San Francisco, California.

Quan Dong Nguyen and David M. Brown contributed equally to this work.

*A list of members of the RISE and RIDE Research Group is available at http://aaojournal.org.

Presented at: the 34th Annual Macula Society Meeting, March 9–12, 2011, Boca Raton, Florida; The Annual Meeting of the Association for Research in Vision and Ophthalmology, May 1–5, 2011, Fort Lauderdale, Florida; The 11th EURETINA Meeting, May 26–29, 2011, London, England; The American Diabetes Association's 71st Scientific Sessions, June 24–28, 2011, San Diego, California; Annual Meeting of the American Society of Retina Specialists, August 20–24, 2011, Boston, Massachusetts; and the 115th Annual Meeting of the American Academy of Ophthalmology, October 22–25, 2011, Orlando, Florida.

Financial Disclosure(s):
The authors have made the following disclosures:

Quan Dong Nguyen – Grants to investigator's institution – Genentech, Inc., Regeneron, Pfizer; Consulting fee or honorarium – Santen Pharmaceutical Co. Ltd., Bausch & Lomb; Board membership – Genentech, Inc.; Consultancy – Santen Pharmaceutical Co. Ltd., Bausch & Lomb.

David M. Brown – Grants to investigator's institution – Genentech, Inc., Regeneron, Novartis, Alcon, Allergan, Alimera, Eli Lilly, Molecular Partners, Ophthotech, Abbott, Schering Plough, Othera Pharmaceuticals, Paloma Pharmaceuticals, Neurotech, TargeGen, Sirion Therapeutics, Inc., Jerini AG; Consulting fee or honorarium – Genentech, Inc; Support for travel to meetings – Genentech, Inc.; Consultant – Genentech, Inc., Regeneron, Allergan, Alcon, Molecular Partners, Novartis, Oraya Therapeutics, Paloma Pharmaceuticals, Steba Biotech; Speakers bureau – Genentech, Inc.

Dennis M. Marcus – Grants to investigator's institution – Allergan, Eli Lilly, Genentech, Inc., Neovista, Pfizer, Regeneron, ThromboGenics; Steering committee member – Genentech, Inc., Regeneron; Advisory board – Genentech, Inc., Regeneron; Consultant – Genentech, Inc.

David S. Boyer – Consultant – Alcon, Allergan, Eyetech, Genentech, Inc., Novartis/QLT, Neurotech, Pfizer, Regeneron; Speakers bureau – Alcon, Allergan, Genentech, Inc., Pfizer; Clinical research projects – Alcon, Allergan, Genentech, Inc., Pfizer, Regeneron.

Sunil Patel – Grants to investigator's institution – Alcon, Allergan, Alimera, Genentech, Inc., Pfizer, Ophthotech, Regeneron; Consulting fee and fees for participation in review activities or honorarium – Genentech, Inc.; Consultant – Allergan, Ophthotech; Speakers bureau – Alcon; Stock/stock options – Ophthotech.

Leonard Feiner – Consultant – Genentech, Inc.; Speakers bureau – Genentech, Inc.

Andrea Gibson – Employee – Genentech, Inc., a member of the Roche Group, and holds equity and/or options in Roche.

Judy Sy – Employee – Genentech, Inc., a member of the Roche Group, and holds equity and/or options in Roche.

Amy Chen Rundle – Employee – Genentech, Inc., a member of the Roche Group, and holds equity and/or options in Roche.

J. Jill Hopkins – Employee – Genentech, Inc., a member of the Roche Group, and holds equity and/or options in Roche.

Roman G. Rubio – Employee – Genentech, Inc., a member of the Roche Group, and holds equity and/or options in Roche.

Jason S. Ehrlich – Employee – Genentech, Inc., a member of the Roche Group, and holds equity and/or options in Roche.

Sponsored by Genentech, Inc. The sponsor worked closely with an investigator steering committee to address matters such as study design and patient recruitment and retention. The sponsor participated in design and conduct of the studies, data collection, analysis, and interpretation of results, and preparation, review, and approval of the manuscript. Support for third-party writing assistance by Ivo Stoilov, MD, CMPP of Envision Scientific Solutions was provided by Genentech, Inc.

Correspondence:
David M. Brown, MD, Retina Consultants of Houston, 6560 Fannin, Suite 750, Houston, TX 77030. E-mail: dmbmd@houstonretina.com.

REGENERON

February 18, 2010

VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients With Diabetic Macular Edema

- Statistically significant improvement in vision achieved over 24 weeks - Results to be presented at Angiogenesis 2010: Clinical Trials meeting in Miami, Florida on February 20, 2010

TARRYTOWN, N.Y. and LEVERKUSEN, Germany, Feb 18, 2010 /PRNewswire via COMTEX News Network/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) and Bayer HealthCare AG today announced that VEGF Trap-Eye showed positive results in a Phase 2 study in patients with diabetic macular edema (DME). The primary endpoint of the study, a statistically significant improvement in visual acuity over 24 weeks compared to the standard of care in DME, macular laser therapy, was met. Visual acuity improvement was measured by the mean number of letters gained over the initial 24 weeks of the study.

"The ability of VEGF Trap-Eye to significantly improve vision in patients with DME in this initial Phase 2 study is encouraging," said Dr. Kemal Malik, member of the Bayer HealthCare Executive Committee responsible for global development. "Bayer and Regeneron will discuss the next steps in further developing VEGF Trap-Eye in this indication."

"The magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this Phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high levels of vascular endothelial growth factor (VEGF) are present," said Diana Do, MD, the Principal Investigator for the study and Assistant Professor of Ophthalmology at the Wilmer Eye Institute, The Johns Hopkins University School of Medicine in Baltimore, Maryland.

Patients in each of the four dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean improvements in visual acuity (8.5 to 11.4 letters of vision gained) compared to patients receiving macular laser therapy (2.5 letters gained) at week 24 ($p < 0.01$ for each VEGF Trap-Eye group versus laser). VEGF Trap-Eye was generally well tolerated, and there were no drug-related serious adverse events.

The results of the Phase 2 study will be presented at the Angiogenesis 2010: Clinical Trials meeting on February 20, 2010 in Miami, Florida. Slides summarizing the data presented will be made available at that time on the Regeneron website (www.regeneron.com on the Presentations Page, under the Investor Relations section).

About the Phase 2 Study Results

In this double-masked, prospective, randomized, multi-center Phase 2 trial, entitled **DA VINCI** (**D**ME **A**nd **V**EGF Trap-Eye: **IN**vestigation of **C**linical Impact), 219 patients with clinically significant DME with central macular involvement were randomized to five groups. The control group received macular laser therapy at week one, and patients were eligible for repeat laser treatments, but no more frequently than at 16 week intervals. Two groups received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye throughout the 6-month dosing period. Two groups received three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by either every 8-week dosing or as-needed (PRN) dosing with specific repeat dosing criteria. The following summarizes the mean gain in visual acuity at week 24 by dosing arm and the mean number of treatments received by patients over the first six monthly visits:

- Standard-of-care macular laser therapy (n=44; 1.7 treatments): +2.5 letters gained
- VEGF Trap Eye 0.5 mg monthly (n=44; 5.6 injections): +8.6 letters gained
- VEGF Trap-Eye 2 mg monthly (n=44; 5.5 injections): +11.4 letters gained
- VEGF Trap-Eye 2 mg every other month, following 3 monthly injections (n=42: 3.8 injections): +8.5 letters gained
- VEGF Trap-Eye 2 mg as-needed, following 3 monthly injections (n=45; 4.4 injections): +10.3 letters gained

The study was not designed to evaluate statistical differences among the results achieved in each of the VEGF Trap-Eye groups, and no significant differences were observed. Over 90 percent of the VEGF Trap-Eye patients and the laser patients remained in the study at the 6-month primary endpoint evaluation.

VEGF Trap-Eye was generally well-tolerated, and there were no ocular or non-ocular drug-related serious adverse events reported in the study. The adverse events reported were those typically associated with intravitreal injections or the underlying disease. The most frequent adverse events reported among patients receiving VEGF Trap-Eye included conjunctival hemorrhage, eye pain, floaters (myodesopsia), ocular redness (hyperemia), and increased intraocular pressure. There were three deaths among the 175 patients treated with VEGF Trap-Eye and none in the 44 patients treated with laser over 6 months. All three patients had underlying risk factors for their cause of death, and the cases were not reported to be drug-

related.

Following the initial 24 weeks of treatment, patients continue to be treated for another 24 weeks on the same dosing regimens. Initial one-year results will be available later this year. Regeneron and Bayer HealthCare are sponsors of the DA VINCI study.

About Diabetic Macular Edema (DME)

Diabetic macular edema (DME) is the most prevalent cause of moderate vision loss in patients with diabetes. DME is a common complication of Diabetic Retinopathy (DR), a disease affecting the blood vessels of the retina. Clinically significant DME is a leading cause of blindness in younger adults (under 50). Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness.

Approximately 370,000 Americans currently suffer from clinically significant DME, with 95,000 new cases arising each year. According to the American Diabetes Association, more than 18 million Americans currently suffer from diabetes, and many other people are at risk for developing diabetes. With the incidence of diabetes steadily climbing, it is projected that up to 10 percent of all patients with diabetes will develop DME during their lifetime.

About VEGF Trap-Eye

VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors.

VEGF Trap-Eye is currently in Phase 3 development in wet (age-related) macular degeneration (AMD). The **VIEW 1** (**V**EGF Trap-Eye: **I**nvestigation of **E**fficacy and Safety in **W**et AMD) study is being conducted in the United States and Canada by Regeneron and the **VIEW 2** study is being conducted in Europe, Asia Pacific, Japan, and Latin America by Bayer HealthCare. The primary endpoint of these non-inferiority studies is the proportion of patients treated with VEGF Trap-Eye who maintain vision at the end of one year, compared to ranibizumab patients. Patient enrollment has been completed in both studies with initial year-one primary endpoint data expected in the second half of 2010.

VEGF Trap-Eye is also in Phase 3 development for the treatment of central retinal vein occlusion (CRVO), another major cause of blindness. The **COPERNICUS** (**CO**ntrolled **P**hase 3 **E**valuation of **R**epeated i**N**travitreal administration of VEGF Trap-Eye **I**n **C**entral retinal vein occlusion: **U**tility and **S**afety) study is being led by Regeneron, and the **GALILEO** (**G**eneral **A**ssessment **L**imiting **I**nfi**L**tration of **E**xudates in central retinal vein **O**cclusion with VEGF Trap-Eye) study is being led by Bayer HealthCare. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. Initial data from the CRVO program are anticipated in early 2011.

About Regeneron Pharmaceuticals, Inc.

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST(R) (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, age-related macular degeneration, and certain cancers. Additional therapeutic candidates are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Forward Looking Statement - Regeneron

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2008 and Form 10-Q for the quarter ending September 30, 2009. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

About Bayer HealthCare Pharmaceuticals

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subsidiary of Bayer AG, is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Bayer Schering Pharma, Consumer Care and Medical Care divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Find more information at www.bayerhealthcare.com.

Forward-Looking Statements - Bayer HealthCare AG

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Contact Information:
Regeneron Pharmaceuticals, Inc.

Peter Dworkin
Investor Relations
914.345.7640
peter.dworkin@regeneron.com

Laura Lindsay
Media Relations
914.345.7800
laura.lindsay@regeneron.com

Bayer HealthCare
Anna Koch,
+49 30 468-15942
anna.koch@bayerhealthcare.com

SOURCE Regeneron Pharmaceuticals, Inc.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2006 VOL. 355 NO. 14

Ranibizumab for Neovascular Age-Related Macular Degeneration

Philip J. Rosenfeld, M.D., Ph.D., David M. Brown, M.D., Jeffrey S. Heier, M.D., David S. Boyer, M.D., Peter K. Kaiser, M.D., Carol Y. Chung, Ph.D., and Robert Y. Kim, M.D., for the MARINA Study Group*

ABSTRACT

BACKGROUND

Ranibizumab — a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A — has been evaluated for the treatment of neovascular age-related macular degeneration.

METHODS

In this multicenter, 2-year, double-blind, sham-controlled study, we randomly assigned patients with age-related macular degeneration with either minimally classic or occult (with no classic lesions) choroidal neovascularization to receive 24 monthly intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) or sham injections. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

RESULTS

We enrolled 716 patients in the study. At 12 months, 94.5% of the group given 0.3 mg of ranibizumab and 94.6% of those given 0.5 mg lost fewer than 15 letters, as compared with 62.2% of patients receiving sham injections ($P<0.001$ for both comparisons). Visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the sham-injection group ($P<0.001$ for both doses). Mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group ($P<0.001$ for both comparisons). The benefit in visual acuity was maintained at 24 months. During 24 months, presumed endophthalmitis was identified in five patients (1.0%) and serious uveitis in six patients (1.3%) given ranibizumab.

CONCLUSIONS

Intravitreal administration of ranibizumab for 2 years prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult (with no classic lesions) choroidal neovascularization secondary to age-related macular degeneration. (ClinicalTrials.gov number, NCT00056836.)

From the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami (P.J.R.); Vitreoretinal Consultants, Methodist Hospital, Houston (D.M.B.); Ophthalmic Consultants of Boston, Boston (J.S.H.); Retina Vitreous Associates Medical Group, Los Angeles (D.S.B.); the Cole Eye Institute, Cleveland Clinic Foundation, Cleveland (P.K.K.); and Genentech, South San Francisco, CA (C.Y.C., R.Y.K.). Address reprint requests to Dr. Rosenfeld at the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami Miller School of Medicine, 900 NW 17th St., Miami, FL 33136, or at prosenfeld@med.miami.edu.

*Principal investigators in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) Study Group are listed in the Appendix.

N Engl J Med 2006;355:1419-31.

AGE-RELATED MACULAR DEGENERATION is a leading cause of irreversible blindness among people who are 50 years of age or older in the developed world.[1-3] The neovascular form of the disease usually causes severe vision loss and is characterized by the abnormal growth of new blood vessels under or within the macula, the central portion of the retina responsible for high-resolution vision.

Neovascularization in this disease is classified by fluorescein angiography into major angiographic patterns termed classic and occult, which may be associated with various degrees of aggressiveness of disease, vision loss, and response to various treatment options.[4] Pharmacologic therapies for neovascular disease that are available in the United States and Europe include verteporfin photodynamic therapy[5-8] — approved by the Food and Drug Administration only for predominantly classic lesions (in which 50% or more of the lesion consists of classic choroidal neovascularization) and by the European Agency for the Evaluation of Medicinal Products for both predominantly classic lesions and occult disease with no classic lesions — and pegaptanib sodium.[9] Both treatments can slow the progression of vision loss, but only a small percentage of treated patients show improvement in visual acuity.

The age-related changes that stimulate pathologic neovascularization are incompletely understood, but vascular endothelial growth factor A (VEGF-A) — a diffusible cytokine that promotes angiogenesis and vascular permeability — has been implicated as an important factor promoting neovascularization.[10-15] Multiple biologically active forms of VEGF-A are generated by alternative messenger RNA splicing and proteolytic cleavage,[16] and two isoforms have been detected in choroidal neovascular lesions.[15]

Ranibizumab — a recombinant, humanized monoclonal antibody Fab that neutralizes all active forms of VEGF-A — was recently approved by the Food and Drug Administration for the treatment of all angiographic subtypes of subfoveal neovascular age-related macular degeneration. In phase 1 and 2 clinical studies, ranibizumab demonstrated encouraging signs of biologic activity, with acceptable safety, when administered intravitreally for up to 6 months in patients with neovascular age-related macular degeneration.[17-19] In our phase 3 study, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA), we evaluated ranibizumab for the treatment of minimally classic or occult with no classic choroidal neovascularization associated with age-related macular degeneration.

METHODS

STUDY DESIGN

At 96 sites in the United States, we enrolled 716 patients in our 2-year, prospective, randomized, double-blind, sham-controlled study of the safety and efficacy of repeated intravitreal injections of ranibizumab among patients with choroidal neovascularization associated with age-related macular degeneration. We performed a prespecified primary efficacy analysis at 12 months. The primary efficacy end point was the proportion of patients who had lost fewer than 15 letters (approximately 3 lines) from baseline visual acuity, as assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, with the use of standardized refraction and testing protocol at a starting test distance of 2 m. We obtained approval from the institutional review board at each study site before the enrollment of patients; all study sites complied with the requirements of the Health Insurance Portability and Accountability Act. The eligibility of lesions was confirmed by an independent central reading center with the use of standardized criteria and trained graders who were unaware of patients' treatment assignments. Patients provided written informed consent before determination of their full eligibility. Screening lasted as long as 28 days.

To be included in the study, patients had to be at least 50 years old; have a best corrected visual acuity of 20/40 to 20/320 (Snellen equivalent determined with the use of an ETDRS chart); have primary or recurrent choroidal neovascularization associated with age-related macular degeneration, involving the foveal center; have a type of lesion that had been assessed with the use of fluorescein angiography and fundus photography as minimally classic or occult with no classic choroidal neovascularization; have a maximum lesion size of 12 optic-disk areas (1 optic-disk area equals 2.54 mm^2 on the basis of 1 optic-disk diameter of 1.8 mm), with neovascularization composing 50% or more of the entire lesion; and have presumed recent progression of disease, as evidenced by observable blood, recent vision loss, or a recent increase in a lesion's greatest linear

diameter of 10% or more. (For a complete list of eligibility criteria, see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org.) There were no exclusion criteria regarding preexisting cardiovascular, cerebrovascular, or peripheral vascular conditions.

STUDY TREATMENT

We randomly assigned eligible patients in a 1:1:1 ratio to receive ranibizumab (Lucentis, Genentech) at a dose of either 0.3 mg or 0.5 mg or a sham injection monthly (within 23 to 37 days) for 2 years (24 injections) in one eye. The evaluating physician was unaware of the patient's treatment assignment; the physician who administered the injection was aware of the patient's treatment assignment regarding ranibizumab or sham treatment but was unaware of the dose of ranibizumab. Other personnel at each study site (except for those assisting with injections), patients, and personnel at the central reading center were unaware of the patient's treatment assignment.

Verteporfin photodynamic therapy was allowed if the choroidal neovascularization in the study eye became predominantly classic. On the basis of a policy decision by the Centers for Medicare and Medicaid Services to reimburse photodynamic therapy for small, minimally classic, and occult lesions as of April 1, 2004, the study protocol was amended to allow photodynamic therapy for minimally classic or occult disease with no classic lesions that were no larger than 4 optic-disk areas and were accompanied by a loss of 20 letters or more from baseline visual acuity, as confirmed at consecutive study visits. (A score of 55 letters is approximately equal to a Snellen equivalent of 20/80 vision.)

The study was designed and analyzed by a committee composed of both academic investigators and representatives of the industry sponsor. In the analysis of the data and the writing of the manuscript, Dr. Rosenfeld had full and unrestricted access to the data, and all the coauthors contributed to the interpretation of the data and the final version of the manuscript. All the authors vouch for the accuracy and completeness of the reported data.

STATISTICAL ANALYSIS

We performed efficacy analyses on an intention-to-treat basis among all patients with the use of a last-observation-carried-forward method for missing data. For all pairwise comparisons, the statistical model adjusted for baseline score for visual acuity (<55 letters vs. ≥55 letters) and subtype of choroidal neovascularization (minimally classic vs. occult with no classic disease). Between-group comparisons for dichotomous end points were performed with the use of the Cochran chi-square test.[20] Change from baseline visual acuity was analyzed with the use of analysis-of-variance models. For end points for lesion characteristics, analysis-of-covariance models adjusting for the baseline value were used. The Hochberg–Bonferroni multiple-comparison procedure[21] was used to adjust for the two pairwise treatment comparisons for the primary end point. Safety analyses included all treated patients.

We determined the number of patients in each group on the basis of a 1:1:1 randomization ratio, Pearson's chi-square test for the two pairwise comparisons of the primary end point, and the Hochberg–Bonferroni multiple comparison procedure at an overall type I error of 0.0497 (adjusting for the three planned safety interim analyses before the primary efficacy analysis). Monte Carlo simulations were used to evaluate the power of the study. We estimated that the enrollment of 720 patients would provide the study with a statistical power of 95% to detect a significant difference between one or both ranibizumab groups and the sham-injection group in the proportion of patients losing fewer than 15 letters at 12 months, assuming a proportion of 65% in each ranibizumab group and 50% in the sham-injection group. (For more details, see the Methods section of the Supplementary Appendix.)

RESULTS

STUDY PATIENTS

Between March 2003 and December 2003, 716 patients were enrolled and randomly assigned to study treatment. Groups were balanced for demographic and baseline ocular characteristics (Table 1).

More than 90% of patients in each treatment group remained in the study at 12 months, and approximately 80 to 90% remained at 24 months (Table 2 of the Supplementary Appendix). The percentages who were still receiving study treatment were similarly high at 12 months and at the end of the study. After the unmasking of first-year results and discussion with the data and safety monitoring committee, ranibizumab was

Table 1. **Baseline Characteristics of the Patients.***

Characteristic	Sham Injection (N = 238)	0.3 mg of Ranibizumab (N = 238)	0.5 mg of Ranibizumab (N = 240)
Sex — no. (%)			
Male	79 (33.2)	85 (35.7)	88 (36.7)
Female	159 (66.8)	153 (64.3)	152 (63.3)
Race — no. (%)†			
White	231 (97.1)	229 (96.2)	232 (96.7)
Other	7 (2.9)	9 (3.8)	8 (3.3)
Age — yr			
Mean	77±7	77±8	77±8
Range	56–94	52–95	52–93
Age group — no. (%)			
50–64 yr	11 (4.6)	13 (5.5)	16 (6.7)
65–74 yr	67 (28.2)	64 (26.9)	64 (26.7)
75–84 yr	132 (55.5)	130 (54.6)	124 (51.7)
≥85 yr	28 (11.8)	31 (13.0)	36 (15.0)
Previous therapy for age-related macular degeneration — no. (%)			
Any treatment	135 (56.7)	140 (58.8)	139 (57.9)
Laser photocoagulation	22 (9.2)	13 (5.5)	14 (5.8)
Medication‡	3 (1.3)	1 (0.4)	3 (1.2)
Nutritional supplements	121 (50.8)	134 (56.3)	127 (52.9)
Other	8 (3.4)	3 (1.3)	3 (1.2)
No. of letters as measure of visual acuity§			
Mean	53.6±14.1	53.1±12.9	53.7±12.8
<55 — no. (%)	109 (45.8)	115 (48.3)	117 (48.8)
≥55 — no. (%)	129 (54.2)	123 (51.7)	123 (51.2)

offered to all patients in October 2005, 2 months before the end of the last patient's final study visit at 24 months. Of the patients in the sham-injection group, 12 were switched to receive 0.5 mg of ranibizumab: 5 patients (2.1%) at 22 months and 7 (2.9%) at 23 months, the last possible injection visit. During the 2-year treatment period, 38 patients in the sham-injection group (16.0%), 2 patients in the group receiving 0.3 mg of ranibizumab (0.8%), and none in the group receiving 0.5 mg of ranibizumab received verteporfin photodynamic therapy at least once. In the second year, 13 patients (5.5%) in the sham-injection group and none in the ranibizumab groups chose to discontinue study treatment and receive pegaptanib sodium, which was approved in the United States in December 2004 for the treatment of neovascular age-related macular degeneration. Of these 13 patients, 8 remained in the follow-up group at 24 months.

PRIMARY AND SECONDARY END POINTS

The primary and key secondary efficacy results at 12 months (prespecified primary analysis) and 24 months are summarized in Figures 1 and 2. The study met its primary end point (Fig. 1A) at 12 months. Of the patients who were treated with ranibizumab, 94.5% of the patients receiving 0.3 mg and 94.6% of those receiving 0.5 mg had lost fewer than 15 letters from baseline visual acuity, as compared with 62.2% in the sham-injection group ($P<0.001$ for the comparison of each dose with the sham-injection group). At 24 months, this end point was met by 92.0% of the patients receiving 0.3 mg of ranibizumab and 90.0% of those receiving 0.5 mg, as compared with 52.9%

Table 1. (Continued.)

Characteristic	Sham Injection (N=238)	0.3 mg of Ranibizumab (N=238)	0.5 mg of Ranibizumab (N=240)
Visual acuity (approximate Snellen equivalent) — no. (%)§			
20/200 or worse	32 (13.4)	35 (14.7)	31 (12.9)
Better than 20/200 but worse than 20/40	170 (71.4)	176 (73.9)	173 (72.1)
20/40 or better	36 (15.1)	27 (11.3)	36 (15.0)
Type of choroidal neovascularization — no. (%)			
Occult with no classic lesion	151 (63.4)	151 (63.4)	149 (62.1)
Minimally classic lesion	87 (36.6)	86 (36.1)	91 (37.9)
Predominantly classic lesion	0	1 (0.4)	0
Missing data	1 (0.4)	0	0
Size of lesion — optic-disk area¶			
Mean	4.4±2.5	4.3±2.5	4.5±2.6
Range	0.0–11.8	0.1–11.8	0.3–12.0
Size of choroidal neovascularization — optic-disk area¶			
Mean	4.3±2.4	4.1±2.5	4.3±2.5
Range	0.0–11.8	0.0–11.8	0.1–12.0
Size of leakage from choroidal neovascularization plus staining of retinal pigment epithelium — optic-disk area¶			
Mean	3.5±2.5	3.6±2.5	3.5±2.6
Range	0.0–12.9	0.0–12.0	0.0–13.5

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was determined by the investigators.
‡ Medications included triamcinolone acetonide, prednisolone ophthalmic, and diclofenac sodium.
§ Visual acuity was measured with the use of ETDRS charts at a starting distance of 2 m. A score of 55 letters is approximately equal to a Snellen equivalent of 20/80.
¶ One optic-disk area is equal to 2.54 mm^2 on the basis of one optic-disk diameter of 1.8 mm.

in the sham-injection group (P<0.001 for each comparison). The visual-acuity benefit associated with ranibizumab was independent of the size of the baseline lesion, the lesion type, or baseline visual acuity (Fig. 1B and 1C).

At 12 and 24 months, approximately one quarter of patients treated with 0.3 mg of ranibizumab and one third of patients treated with 0.5 mg of ranibizumab had gained 15 or more letters in visual acuity, as compared with 5.0% or less of those in the sham-injection group (P<0.001 for each comparison) (Fig. 1D).

At both doses of ranibizumab, the mean improvement from baseline in visual-acuity scores was evident 7 days after the first injection (P=0.006 for the 0.3-mg dose and P=0.003 for the 0.5-mg dose), whereas mean visual acuity in the sham-injection group declined steadily over time at each monthly assessment (P<0.001 for both comparisons) (Fig. 2A). At 12 months, mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group (P<0.001 for both comparisons). The benefit in visual acuity was maintained at 24 months. The average benefit associated with ranibizumab over that of sham injection was approximately 17 letters in each dose group at 12 months and 20 to 21 letters at 24 months.

At baseline, the percentages of patients with 20/40 vision or better were similar among the three groups (Fig. 2B). At 12 months, approximately 40% of patients receiving ranibizumab had 20/40 vision or better, as compared with 11.3% in the sham-injection group (P<0.001). At 24 months, of the patients receiving ranibizumab, 34.5% of

those in the 0.3-mg group and 42.1% in the 0.5-mg group had at least 20/40 vision, whereas the proportion in the sham-injection group had dropped to 5.9% (P<0.001 for each comparison).

A single patient in the sham-injection group had 20/20 or better vision at baseline. Among patients receiving ranibizumab, 3.8% in the 0.3-mg group and 7.9% in the 0.5-mg group had 20/20 vision or better at 12 months, and 6.7% in the 0.3-mg group and 7.9% in the 0.5-mg group had 20/20 vision or better at 24 months. In the sham-injection group, only two patients (0.8%) had 20/20 vision or better at 12 months (P<0.001 for the comparison with the 0.5-mg group and P=0.03 for the comparison with the 0.3-mg group), and one (0.4%) had 20/20 vision or better at 24 months (P<0.001 for the comparison with each ranibizumab group).

The percentages of patients with visual acuity of 20/200 or worse were similar among the three groups at baseline (Fig. 2C). At 12 and 24 months, the percentages in the ranibizumab-treated groups remained about the same, whereas the percentages in the sham-injection group had increased by 3 to 3.5 times (P<0.001 for the comparison with each ranibizumab dose at 12 and 24 months). Very few patients receiving ranibizumab had severe vision loss (30 letters or more) from baseline (0.8% of the 0.3-mg group and 1.2% of the 0.5-mg group), as compared with 14.3% of the sham-injection group at 12 months; at 24 months, 3.4% of the 0.3-mg group and 2.5% of the 0.5-mg group had severe vision loss, as compared with 22.7% of the sham-injection group (P<0.001 for the comparison with each dose at 12 and 24 months).

Ranibizumab treatment was associated with arrested growth of and leakage from choroidal neovascularization (including intense, progressive staining of the retinal pigment epithelium) (Fig. 3A through Fig. 3D). The mean change from baseline in each of the ranibizumab-treated groups differed significantly from that in the sham-injection group at 12 and 24 months (P<0.001 for each comparison).

Figure 1 (facing page). **Rate of Loss or Gain of Visual Acuity at 12 and 24 Months Associated with Ranibizumab, as Compared with Sham Injection.**

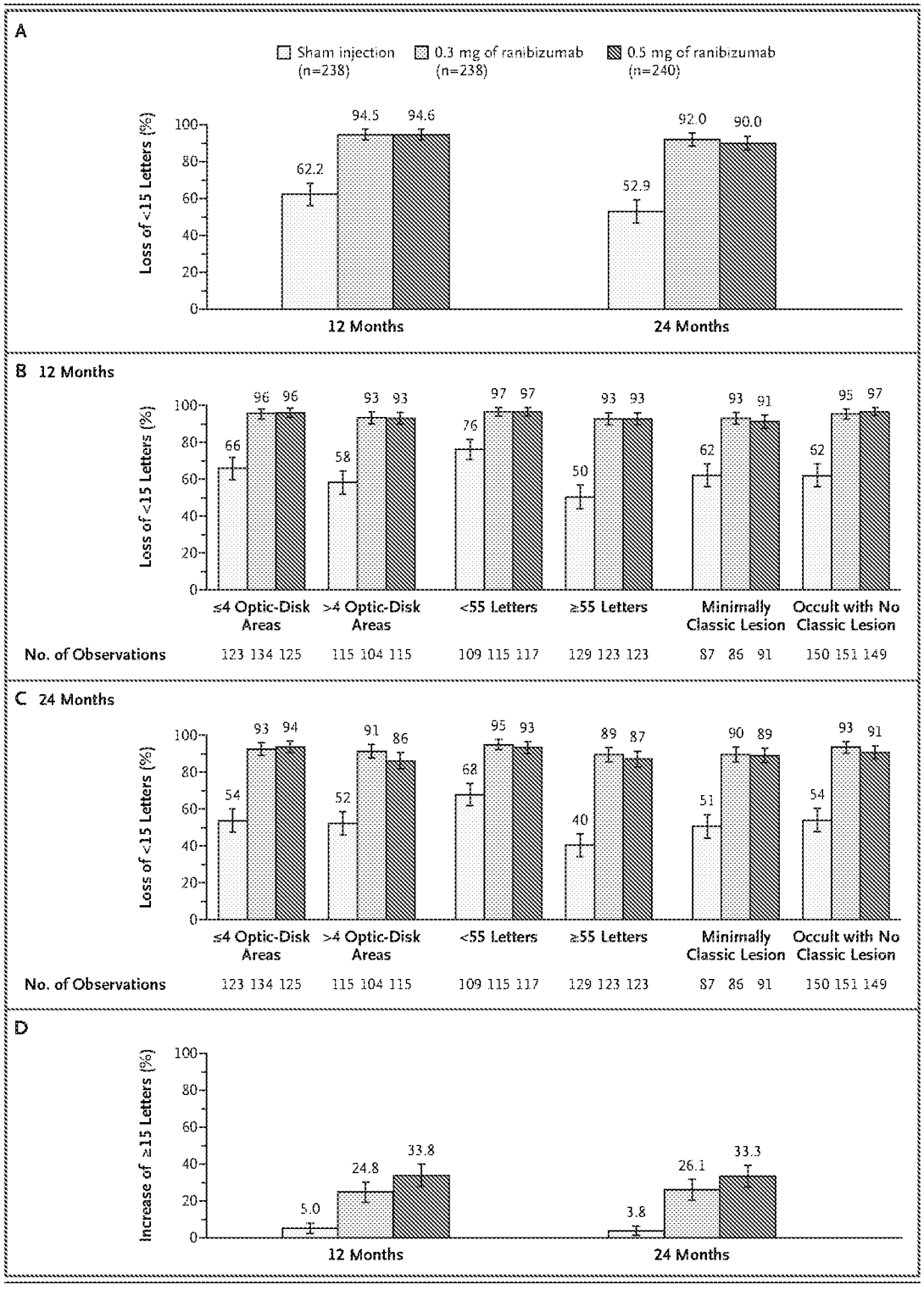
Panel A shows the percentage of patients in each group who lost fewer than 15 letters from baseline visual acuity at 12 months (the primary efficacy end point) and at 24 months. Panels B and C summarize the percentage of patients who lost fewer than 15 letters at 12 and 24 months, respectively, according to lesion size (1 optic-disk area is equal to 2.54 mm^2 on the basis of 1 optic-disk diameter of 1.8 mm), baseline visual acuity (a score of 55 letters is approximately equal to a Snellen equivalent of 20/80), and lesion type. Panel D shows the percentage of patients who gained 15 or more letters from baseline at 12 and 24 months. For the study overall, treatment comparisons were based on the Cochran chi-square test stratified according to the visual-acuity score at day 0 (<55 letters vs. ≥55 letters) and choroidal neovascularization subtype. Pearson's chi-square test was used for treatment comparisons in each subgroup. The last-observation-carried-forward method was used to handle missing data. All tests were two-sided (P<0.001 for all comparisons between each ranibizumab group and the sham-injection group). I bars represent 95% confidence intervals.

ADVERSE EVENTS

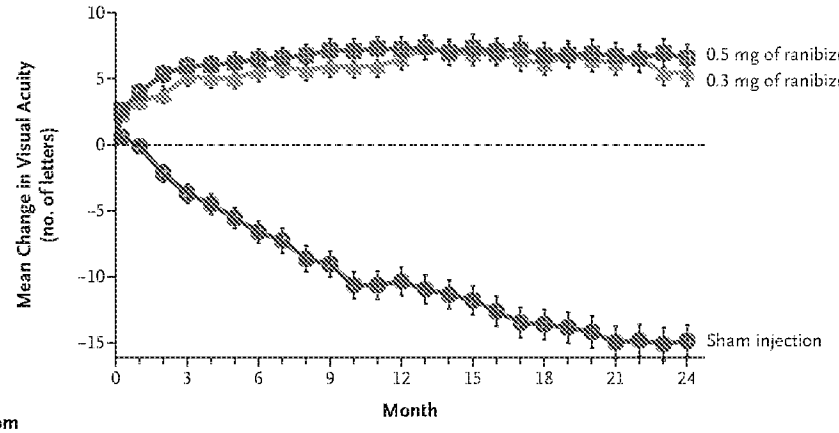
Cumulative adverse events for the 24-month study period are summarized in Table 2. Each of the key serious ocular adverse events occurred in different patients (Table 3 of the Supplementary Appendix). Investigator-reported cases of endophthalmitis, as well as any case of serious uveitis treated with intravitreal antibiotics, were presumed to be endophthalmitis. The presumed endophthalmitis rate was 5 of 477 patients (1.0%) or, alternatively, a rate per injection of 0.05% (5 of 10,443 total injections). In four of the five presumed cases of endophthalmitis, neither vitreous nor aqueous culture showed growth.

Slit-lamp examination revealed inflammation (of any cause, including endophthalmitis) throughout the study in the ranibizumab groups (Table 2, and Table 4 and 5 of the Supplementary Appendix).[22,23] Most of the inflammation in all groups was designated as trace or 1+.

Ranibizumab had no long-term effect on intraocular pressure, on average, as assessed by monthly preinjection measurements during the 2-year follow-up. Intraocular pressure was increased on average 1 hour after ranibizumab injections at protocol-mandated intraocular-pressure assessments; however, the absence of corresponding changes in preinjection measurements suggests the postinjection increases were transient. On average, postinjection intraocular pressure increased from the preinjection value by 1.9 to 3.5 mm Hg in the 0.3-mg group and 2.1 to 3.4 mm Hg

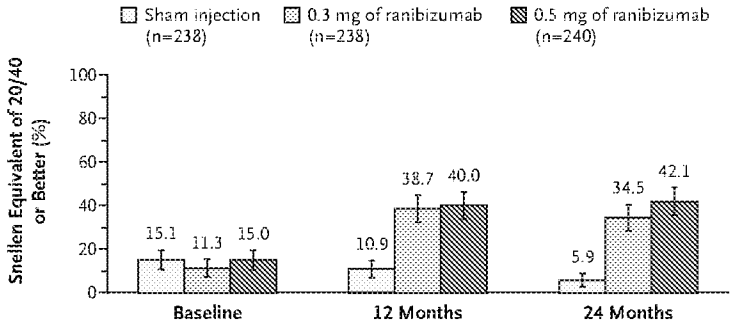


A



Mean Change from Baseline	(day 7)								
0.5 mg of ranibizumab	+2.6	+5.9	+6.5	+7.2	+7.2	+7.4	+6.8	+6.7	+6.6
0.3 mg of ranibizumab	+2.3	+5.1	+5.6	+5.9	+6.5	+6.9	+6.1	+6.2	+5.4
Sham injection	+0.6	−3.7	−6.6	−9.1	−10.4	−11.8	−13.6	−15.0	−14.9

B



C

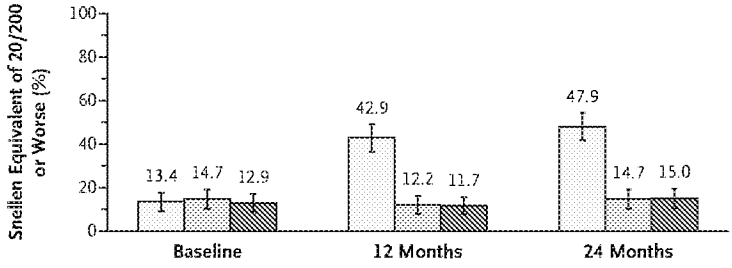


Figure 2. **Mean Changes from Baseline in Visual Acuity and Snellen Equivalents at 12 and 24 Months.**

Panel A shows the mean changes from baseline in visual acuity during a 24-month period. At each monthly assessment, $P<0.001$ for the comparison between each ranibizumab group and the sham-injection group. On day 7, $P=0.006$ for patients receiving 0.3 mg of ranibizumab and $P=0.003$ for those receiving 0.5 mg. Panels B and C show the change from baseline in the percentage of patients with a Snellen equivalent of 20/40 or better and the percentage of patients with 20/200 or worse, respectively, at 12 and 24 months ($P<0.001$ for the comparison between each ranibizumab group and the sham-injection group at 12 and 24 months). Treatment comparisons use pairwise models adjusted for visual-acuity scores at day 0 (<55 letters vs. ≥55 letters) and for the type of choroidal neovascularization. Analysis of variance was used to assess the change in visual acuity from baseline at each monthly assessment. The Cochran chi-square test was used for the comparison of percentages. The last-observation-carried-forward method was used to handle missing data. All statistical tests were two-sided. I bars represent SE in Panel A and 95% confidence intervals in Panels B and C.

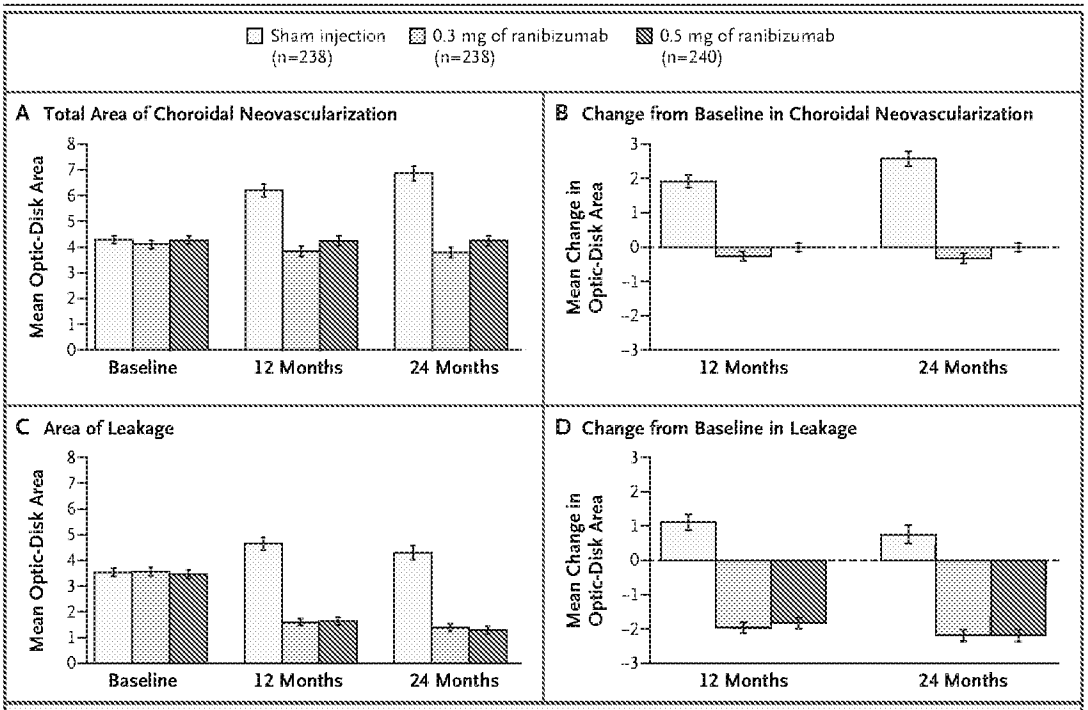


Figure 3. **Mean (±SE) Changes in Choroidal Neovascularization and Leakage.**

Leakage refers to that associated with choroidal neovascularization plus intense, progressive staining of the retinal pigment epithelium. One optic-disk area is equal to 2.54 mm^2. Pairwise analysis of covariance was adjusted for the visual-acuity score at day 0 (<55 letters vs. ≥55 letters), the subtype of choroidal neovascularization, and the baseline value of the end point. Missing data were imputed according to the last-observation-carried-forward approach. P<0.001 for the comparison between each ranibizumab group and the sham-injection group at 12 and 24 months. All statistical tests were two-sided.

in the 0.5-mg group, as compared with 0.8 to 1.5 mm Hg in the sham-injection group. Postinjection intraocular pressure of 30 mm Hg or more occurred in approximately 13.0% of patients in the 0.3-mg group and 17.6% of those in the 0.5-mg group, as compared with 3.4% of those in the sham-injection group. Intraocular pressure of 40 mm Hg or more occurred in 2.3% of patients in each ranibizumab group and in no patients in the sham-injection group. A postinjection intraocular pressure of 50 mm Hg or more occurred in 0.6% of each ranibizumab group.

Ranibizumab was not associated with an increased frequency of cataracts (15.7% of patients in the sham-injection group, as compared with 15.5% in each ranibizumab group). However, lens status did change in a few patients during the 2-year treatment period. Of patients whose study eye was phakic at baseline and whose lens status was known at 24 months, the study eye of 6 of 117 patients in the 0.3-mg group (5.1%) and 8 of 111 patients in the 0.5-mg group (7.2%) had become pseudophakic by 24 months, as compared with no patients in the sham-injection group. At 24 months, ranibizumab-treated patients whose study eye had been phakic and then became pseudophakic during the course of the study had visual acuity similar to that of ranibizumab-treated patients overall.

Seventeen deaths occurred during the 2-year study. In the sham-injection group, six patients (2.5%) died: two from strokes, one from congestive heart failure, one from renal failure, one from acute respiratory failure, and one of an unknown cause. In the group receiving 0.3 mg of ranibizumab, five patients (2.1%) died: two from myocardial infarction, one from complications of non-Hodgkin's lymphoma, one from pneumonia, and one from an unknown cause. In the group receiving 0.5 mg of ranibizumab, six patients (2.5%) died: two from stroke, one from a small-bowel infarct, one from traumatic injury from an automobile accident, one from sepsis, and one from chronic asthma and chronic obstructive pulmonary disease. An additional three patients who had completed the study or had withdrawn from

Table 3. **Adverse Events at 24 Months.***

Adverse Event	Sham Injection (N=236)	0.3 mg of Ranibizumab (N=238)	0.5 mg of Ranibizumab (N=239)
Serious ocular event — no. (%)			
Presumed endophthalmitis†	0	2 (0.8)	3 (1.3)
Culture not obtained	0	1 (0.4)	0
Culture negative	0	1 (0.4)	3 (1.3)‡
Uveitis	0	3 (1.3)	3 (1.3)§
Rhegmatogenous retinal detachment	1 (0.4)	0	0
Retinal tear	0	1 (0.4)	1 (0.4)
Vitreous hemorrhage	2 (0.8)	1 (0.4)	1 (0.4)
Lens damage	0	0	1 (0.4)
Most severe ocular inflammation — no. (%)¶			
None	206 (87.3)	198 (83.2)	189 (79.1)
Trace	24 (10.2)	19 (8.0)	35 (14.6)
1+	6 (2.5)	14 (5.9)	8 (3.3)
2+	0	2 (0.8)	2 (0.8)
3+	0	2 (0.8)	2 (0.8)
4+	0	3 (1.3)	3 (1.3)
Nonocular adverse event			
Investigator-defined hypertension			
No. of patients (%)	38 (16.1)	41 (17.2)	39 (16.3)
Mean decrease in blood pressure from baseline — mm Hg	3.3/3.5	2.6/2.5	4.4/1.1
Key arterial thromboembolic events (nonfatal) — no. (%)			
Myocardial infarction	4 (1.7)	6 (2.5)§	3 (1.3)‖
Stroke	2 (0.8)**††	3 (1.3)‡‡	6 (2.5)‖§§
Death — no. (%)			
Vascular cause (APTC criteria)	4 (1.7)¶¶	3 (1.3)‡‡‖‖	3 (1.3)***
Nonvascular cause	2 (0.8)	2 (0.8)	3 (1.3)
Nonocular hemorrhage — no. (%)			
Total serious and nonserious events	13 (5.5)	22 (9.2)	21 (8.8)
Reported as a serious adverse event	2 (0.8)	3 (1.3)	5 (2.1)

* APTC denotes Antiplatelet Trialists' Collaboration.
† Events were categorized as presumed endophthalmitis in cases in which intravitreal antibiotics were administered.
‡ One event was reported as uveitis by an investigator.
§ One patient had two episodes.
¶ Ocular inflammation (regardless of cause) was determined on the basis of slit-lamp examination.
‖ One patient had a myocardial infarction and a hemorrhagic stroke, both nonfatal.
** One patient in the sham-injection group received a single 0.5-mg dose of ranibizumab in error approximately 8 months before the onset of the stroke.
†† One patient had a second episode of stroke, which resulted in death.
‡‡ One patient had a nonfatal ischemic stroke and died of an unknown cause.
§§ One patient had a cerebral ischemic incident that was categorized as an ischemic stroke.
¶¶ Two patients died from stroke, one from congestive heart failure, and one from an unknown cause.
‖‖ Two patients died from myocardial infarction, and one from an unknown cause.
*** One patient died from a small-bowel infarct, and two from stroke.

the study before 24 months died: one patient in the sham-injection group from cardiac arrest 15 days after completing the study, one in the group receiving 0.3 mg of ranibizumab from lung cancer 174 days after completing the last study visit at 22 months, and one in the group receiving 0.5 mg of ranibizumab from lung cancer 91 days after completing the last study visit at 23 months.

The overall incidence of any serious or nonserious nonocular (systemic) adverse event, including adverse events previously associated with systemically administered anti-VEGF therapy, such as arterial thromboembolic events and hypertension (Table 2), was similar among the groups. At 24 months, on the basis of the classification system of the Antiplatelet Trialists' Collaboration (APTC),[24] which includes nonfatal myocardial infarction, nonfatal stroke, and death from a vascular or unknown cause, the rate of arterial thromboembolic events among patients in the sham-injection group was 3.8%, the rate among patients receiving 0.3 mg of ranibizumab was 4.6%, and the rate among patients receiving 0.5 mg of ranibizumab was 4.6%; none of the differences were significant. The onset of these events and the time of study treatment appeared to be unrelated. No adverse events of proteinuria were reported. Nonocular hemorrhages occurred at similar rates in the first treatment year in the three groups (3.8% in both the sham-injection group and the 0.3-mg group and 2.1% in the 0.5-mg group).

Cumulative rates of nonocular hemorrhage increased in all groups through the second treatment year, but more so in the ranibizumab groups (Table 2). By 24 months, nonocular hemorrhage had occurred in 5.5% of patients in the sham-injection group, as compared with 9.2% of those receiving 0.3 mg of ranibizumab and 8.8% of those receiving 0.5 mg of ranibizumab; none of the differences were significant. (For cumulative rates of specific types of nonocular hemorrhage, see Table 6 of the Supplementary Appendix.) Since the study was not powered to detect small differences in rates, no conclusion can be drawn regarding whether these differences were drug-related or due to chance alone. Among the 12 patients in the sham-injection group who switched to ranibizumab therapy, no serious adverse events were reported after the switch.

Patients in all three groups were tested for circulating antibodies against ranibizumab at baseline and at months 6, 12, and 24. A small percentage of patients in all three groups tested positive before study treatment, possibly owing to preexisting anti-Fab immunoreactivity. At baseline, immunoreactivity rates were 0.9% in the group receiving 0.3 mg of ranibizumab, 0% in the group receiving 0.5 mg of ranibizumab, and 0.5% in the sham-injection group. During the first treatment year, immunoreactivity rates increased similarly in all treatment groups. However, by the end of the second year, 4.4% of patients in the 0.3-mg group and 6.3% of those in the 0.5-mg group tested positive, as compared with only 1.1% in the sham-injection group. Exploratory subgroup analyses of safety and efficacy outcomes revealed no clinically relevant differences between patients with and those without immunoreactivity to ranibizumab.

DISCUSSION

Our phase 3 study (MARINA) of a treatment for neovascular age-related macular degeneration demonstrated not only prevention of vision loss but also a mean improvement in vision in the prespecified primary analysis at 1 year. The efficacy outcomes for patients receiving ranibizumab at 1 year were maintained through the second year, whereas vision in patients in the sham-injection group continued to decline.

Most of the serious ocular adverse events were attributable either to the injection procedure or to ranibizumab. Presumed endophthalmitis was attributed to the injection and serious uveitis to ranibizumab. Although endophthalmitis could not be definitively distinguished from sterile serious uveitis in patients whose inflammation was treated with intravitreal antibiotics but whose vitreous cultures were negative, the rates of these events were on the order of 1 to 2% during the 2-year treatment period.

The three treatment groups did not clearly differ in their rates of nonocular adverse events. The reported nonserious and serious nonocular adverse events reflect common medical conditions in an elderly population. In regard to potential systemic anti-VEGF side effects, the rates of hypertension were not imbalanced, and no adverse events associated with proteinuria were reported. Nonocular hemorrhages were more frequent in the ranibizumab groups than in the sham-injection group. During the 2-year treatment period, the rates of arterial thromboembolic events

(on the basis of APTC criteria) were similar in the three treatment groups. However, our study was not powered to detect small differences between groups in the rates of uncommon adverse events. Additional ongoing clinical trials may provide further information on the rates of key nonocular adverse events. For example, elsewhere in this issue of the *Journal*, Brown et al. report data from the first year of the phase 3 Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study,[25] which compares verteporfin photodynamic therapy with ranibizumab treatment at the same doses used in our study. The results of the ANCHOR study are consistent with those of the first year of our study for both safety and efficacy outcomes in the ranibizumab-treated groups.

The clinical significance of the increased rate of systemic immunoreactivity with ranibizumab treatment, which was not present at 1 year but emerged at 2 years, is unclear. Exploratory analyses failed to reveal any effect of immunoreactivity on efficacy or safety.

In conclusion, ranibizumab therapy was associated with clinically and statistically significant benefits with respect to visual acuity and angiographic lesions during 2 years of follow-up in patients with minimally classic or occult lesions with no classic choroidal neovascularization. These efficacy outcomes were achieved with a low rate of serious ocular adverse events and with no clear difference from the sham-treated group in the rate of nonocular adverse events.

Supported by Genentech and Novartis Pharma.

Dr. Rosenfeld reports having received consulting fees from Genentech, Eyetech, Novartis Ophthalmics, Protein Design Labs, Allergan, BioAxone, Tanox, Genaera, Jerini, Quark, and Athenagen; lecture fees from Genentech, Eyetech, and Novartis Ophthalmics; and grant support from Genentech, Eyetech, and Alcon Laboratories. Dr. Brown reports having received consulting fees from Genentech, Eyetech, Alcon Laboratories, and Allergan; having an equity interest in Pfizer; and having received lecture fees from Eyetech and Pfizer. Dr. Heier reports having received consulting fees from Genentech, Eyetech, Jerini, Oxigene, Allergan, Genzyme, iScience, ISTA, Pfizer, Regeneron, Theragenics, VisionCare, and Novartis; lecture fees from Genentech, Eyetech, Jerini and Allergan; and grant support from Genentech, Eyetech, Pfizer, Theragenics, and Genaera. Dr. Boyer reports having received consulting fees from Genentech, Eyetech, Pfizer, Novartis, QLT, and Regeneron. Dr. Kaiser reports having received consulting fees, lecture fees, and grant support from Genentech and Novartis. Dr. Chung and Dr. Kim report being employees of Genentech and report owning Genentech stock. No other potential conflict of interest relevant to this article was reported.

We are indebted to the patients who participated in this study, their families, and the research teams at each site; to the members of the data and safety monitoring committee: Frederick L. Ferris III, M.D. (chair), Susan B. Bressler, M.D., Stuart L. Fine, M.D., and Marian Fisher, Ph.D.; to the members of the University of Wisconsin Fundus Photograph Reading Center; to the members of the data-coordinating center (Statistics Collaborative); and to Genentech personnel Charles Semba, M.D. and Steven Butler, Ph.D., for their critical comments and review throughout the design, conduct, and analysis of the study; to Susan Schneider, M.D., Nisha Acharya, M.D., and Angele Singh, M.D., for their critical comments and review of the second-year results; and to staff members for their assistance in the preparation of the manuscript.

APPENDIX

The following principal investigators were members of the MARINA Study Group: T. Aaberg, Associated Retinal Consultants, Grand Rapids, MI; P. Abraham, Black Hills Regional Eye Institute, Rapid City, SD; D. Alfaro III, Retina Consultants of Charleston, Charleston, SC; A. Antoszyk, Southeast Clinical Research Associates, Charlotte, NC; C. Awh, Retina Vitreous Associates, Nashville; G. Barile, Edward Harkness Eye Institute, New York; C. Barr, Louisville, KY; W. Bauman, Brooke Army Medical Center, Fort Sam Houston, TX; P. Beer, Lions Eye Institute, Albany, NY; B. Berger, Austin, TX; A. Bhavsar, Retina Center, Minneapolis; R. Bhisitkul, University of California at San Francisco, School of Medicine, San Francisco; H. Boldt, University of Iowa Hospital and Clinics, Iowa City; D. Boyer, Retina–Vitreous Associates, Beverly Hills, CA; W. Bridges, Western Carolina Retinal Associates, Asheville, NC; R. Brod, Lancaster, PA; D. Brown, Vitreoretinal Consultants, Houston; J. Bryan, Associated Retinal Consultants, Phoenix, AZ; R. Chambers, Retinal Consultants, Columbus, OH; T. Ciulla, Midwest Eye Institute, Indianapolis; T. Connor, Medical College of Wisconsin, Milwaukee; S. Cousins, Bascom Palmer Eye Institute, Palm Beach Gardens, FL; R. Dreyer, Northwest Retina, Portland, OR; W. Dunn, Florida Retina Institute, Daytona Beach, FL; D. Eliott, Kresge Eye Institute, Detroit; P. Ferrone, Long Island Vitreoretinal Consultants, Great Neck, NY; B. Foster, New England Retina Consultants, West Springfield, MA; W. Freeman, University of California at San Diego, Jacobs Retina Center, La Jolla; W. Fung, Pacific Eye Associates, San Francisco; R. Gentile, New York Eye and Ear Infirmary, New York; B. Glaser, National Retina Institute, Chevy Chase, MD, and Towson, MD; D. Glaser, Retina Associates of St. Louis, Florissant, MO; L. Glazer, Vitreo-Retinal Associates, Grand Rapids, MI; V. Gonzalez, Valley Retina Institute, McAllen, TX; R. Goodart, Rocky Mountain Retina Consultants, Salt Lake City; J. Haller, Johns Hopkins University, Baltimore; M. Hammer, Retina Associates of Florida, Tampa; J. Heier, Ophthalmic Consultants of Boston, Boston; B. Hubbard, Emory University, Atlanta; H. Hudson, Retina Centers, Tucson, AZ; D. Ie, Delaware Valley Retina Associates, Lawrenceville, NJ; M. Johnson, University of Michigan, Ann Arbor; R. Johnson, West Coast Retina Medical Group, San Francisco; D. Joseph, Barnes Retina Institute, St. Louis; P. Kaiser, Cleveland Clinic Foundation, Cole Eye Institute, Cleveland; R. Kaiser, Retina Diagnostic and Treatment Associates, Philadelphia; R. Katz, K. Kelly, Palm Beach Eye Foundation, Lake Worth, FL; R. Kingsley, Dean A. McGee Eye Institute, Oklahoma City; G. Kokame, Retina Consultants of Hawaii, Aiea, HI; B. Kuppermann, University of California at Irvine, Irvine; S. Leff, Retina-Vitreous Center, Lakewood, NJ, and New Brunswick, NJ; C. Leong, Bay Area Retina Associates, Walnut Creek, CA; L. Lobes, Retina Vitreous Consultants, Pittsburgh; M. Lomeo, Midwest Retina, Columbus, OH; C. MacDonald, University of Texas Health Science Center, San Antonio; D. Marcus, Southeast Retina Center, Augusta, GA; L. Marouf, Retina Associates of South Texas, San Antonio; R. Martidis, Retina Diagnostic and Treatment Associates, Philadelphia; J. Martinez, Austin

Retina Associates, Austin, TX; D. Maxwell, Jr., Retinal Associates of Oklahoma, Oklahoma City; C. McCannel, Mayo Clinic, Rochester, MN; T. McMillan, Southeastern Retina Associates, Knoxville, TN; L. Morse, University of California at Davis Medical Center, Sacramento; T. Oei, Braverman-Terry-Oei Eye Associates, San Antonio, TX; R. Park, University of Arizona, Tucson; M. Paul, Danbury Eye Physicians and Surgeons, Danbury, CT; P. Pavan, University of South Florida, Tampa; D. Pieramici, California Retina Consultants, Santa Barbara, CA; J. Prensky, Pennsylvania Retina Specialists, Camp Hill, PA; D. Quillen, Penn State Hershey Medical Center, Hershey; E. Reichel, New England Eye Center, Boston; W. Rodden, Retina and Vitreous Center of Southern Oregon, Ashland; P. Rosenfeld, Bascom Palmer Eye Institute, Miami; J. Rubio, Retina Associates of South Texas, San Antonio; P. Runge, Ophthalmic Consultants, Sarasota, FL; S. Sadda, Doheny Eye Institute, Los Angeles; G. Sanborn, Virginia Eye Institute, Richmond; R. Sanders, Retina Group of Washington, Chevy Chase, MD; S. Sanislo, California Vitreoretinal Research Center, Menlo Park, CA; S. Schwartz, Bascom Palmer Eye Institute, Palm Beach Gardens, FL; M. Singer, Medical Center Ophthalmology Associates, San Antonio, TX; L. Snady-McCoy, Rhode Island Eye Institute, Providence; S. Sneed, Retinal Consultants of Arizona, Phoenix; J. Stallman, Georgia Retina, Decatur, GA; W. Stern, Northern California Retina–Vitreous Associates, San Mateo and Mountain View; G. Stoller, Ophthalmic Consultants of Long Island, Rockville Centre, NY; B. Taney, Retina Vitreous Consultants, Ft. Lauderdale, FL; J. Thompson, Retina Specialists, Towson, MD; D. Tom, New England Retina Associates, Hamden, CT; M. Trese, Associated Retinal Consultants, Royal Oak, MI; T. Verstaeten, Allegheny General Hospital, Pittsburgh; C. Vu, Retina Associates, Annapolis, MD; J. Walker, Retina Consultants of Southwest Florida, Fort Myers; H. Weiss, Retina Consultants of Michigan, Southfield; J. Weiss, Retina Associates of South Florida, Margate; C. Wells, Vitreoretinal Associates, Seattle; H. Woodcome, Ophthalmology Consultants, Providence, RI; M. Zarbin, New Jersey Medical School, Newark; and K. Zhang, John Moran Eye Center, University of Utah, Salt Lake City.

REFERENCES

1. Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA 2004;291:1900-1.
2. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564-72.
3. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844-51.
4. Barbazetto I, Burdan A, Bressler NM, et al. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment — TAP and VIP report No. 2. Arch Ophthalmol 2003;121:1253-68.
5. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials — TAP report. Arch Ophthalmol 1999;117:1329-45. [Erratum, Arch Ophthalmol 2000;118:488.]
6. Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials — TAP report 2. Arch Ophthalmol 2001;119:198-207.
7. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization — Verteporfin In Photodynamic Therapy (VIP) report 2. Am J Ophthalmol 2001; 131:541-60.
8. Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. Retina 2005;25:119-34.
9. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805-16.
10. Lopez PF, Sippy BD, Lambert HM, Thach AB, Hinton DR. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. Invest Ophthalmol Vis Sci 1996;37:855-68.
11. Frank RN, Amin RH, Eliott D, Puklin JE, Abrams GW. Basic fibroblast growth factor and vascular endothelial growth factor are present in epiretinal and choroidal neovascular membranes. Am J Ophthalmol 1996;122:393-403.
12. Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. Invest Ophthalmol Vis Sci 1996;37:1929-34.
13. Kliffen M, Sharma HS, Mooy CM, Kerkvliet S, de Jong PT. Increased expression of angiogenic growth factors in age-related maculopathy. Br J Ophthalmol 1997;81:154-62.
14. Otani A, Takagi H, Oh H, et al. Vascular endothelial growth factor family and receptor expression in human choroidal neovascular membranes. Microvasc Res 2002;64:162-9.
15. Rakic JM, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci 2003;44:3186-93.
16. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581-611.
17. Rosenfeld PJ, Schwartz SD, Blumenkranz MS, et al. Maximum tolerated dose of a humanized anti-vascular endothelial growth factor antibody fragment for treating neovascular age-related macular degeneration. Ophthalmology 2005;112: 1048-53.
18. Heier JS, Antoszyk AN, Pavan PR, et al. Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. Ophthalmology 2006;113:633-42.
19. Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N. Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age-related macular degeneration. Ophthalmology 2006;113: 623-32.
20. Cochran WG. Some methods for strengthening the common chi-square tests. Biometrics 1954;10:417-51.
21. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800-2.
22. Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47:155-70.
23. Grading of vitreous cells. In: Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. 2nd ed. New York: Mosby, 1996:64.
24. Collaborative overview of randomised trials of antiplatelet therapy — I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308:81-106. [Erratum, BMJ 1994;308:1540.]
25. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432-44.

Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration

The EXCITE Study

*Ursula Schmidt-Erfurth, MD,[1] Bora Eldem, MD,[2] Robyn Guymer, MD, PhD,[3] Jean-François Korobelnik, MD,[4] Reinier O. Schlingemann, MD,[5] Ruth Axer-Siegel, MD,[6] Peter Wiedemann, MD,[7] Christian Simader, MD,[8] Margarita Gekkieva, MD,[9] Andreas Weichselberger, PhD,[9] on behalf of the EXCITE Study Group**

Objective: To demonstrate noninferiority of a quarterly treatment regimen to a monthly regimen of ranibizumab in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Design: A 12-month, multicenter, randomized, double-masked, active-controlled, phase IIIb study.

Participants: Patients with primary or recurrent subfoveal CNV secondary to AMD (353 patients), with predominantly classic, minimally classic, or occult (no classic component) lesions.

Intervention: Patients were randomized (1:1:1) to 0.3 mg quarterly, 0.5 mg quarterly, or 0.3 mg monthly doses of ranibizumab. Treatment comprised of a loading phase (3 consecutive monthly injections) followed by a 9-month maintenance phase (either monthly or quarterly injection).

Main Outcome Measures: Mean change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) from baseline to month 12 and the incidence of adverse events (AEs).

Results: In the per-protocol population (293 patients), BCVA, measured by Early Treatment Diabetic Retinopathy Study-like charts, increased from baseline to month 12 by 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly (104 patients), 0.5 mg quarterly (88 patients), and 0.3 mg monthly (101 patients) dosing groups, respectively. Similar results were observed in the intent-to-treat (ITT) population (353 patients). The mean decrease in CRT value from baseline to month 12 in the ITT population was −96.0 μm in 0.3 mg quarterly, −105.6 μm in 0.5 mg quarterly, and −105.3 μm in 0.3 mg monthly group. The most frequent ocular AEs were conjunctival hemorrhage (17.6%, pooled quarterly groups; 10.4%, monthly group) and eye pain (15.1%, pooled quarterly groups; 20.9%, monthly group). There were 9 ocular serious AEs and 3 deaths; 1 death was suspected to be study related (cerebral hemorrhage; 0.5 mg quarterly group). The incidences of key arteriothromboembolic events were low.

Conclusions: After 3 initial monthly ranibizumab injections, both monthly (0.3 mg) and quarterly (0.3 mg/0.5 mg) ranibizumab treatments maintained BCVA in patients with CNV secondary to AMD. At month 12, BCVA gain in the monthly regimen was higher than that of the quarterly regimens. The noninferiority of a quarterly regimen was not achieved with reference to 5.0 letters. The safety profile was similar to that reported in prior ranibizumab studies.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2010;xx:xxx © 2010 by the American Academy of Ophthalmology.

**Group members listed online in Appendix 1 (available at http://aaojournal.org).*

Vascular endothelial growth factor (VEGF)-A is a key factor involved in the pathogenesis of choroidal neovascularization (CNV).[1–5] Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA) is a recombinant, fully humanized, affinity-matured monoclonal antigen-binding antibody fragment that inhibits the binding of multiple biologically active forms of VEGF-A to their receptors.[6–8]

Two pivotal Phase III trials, MARINA (*M*inimally classic/occult trial of the *A*nti-VEGF antibody *R*anibizumab *I*n the treatment of *N*eovascular *A*ge-related macular degeneration)[9] and ANCHOR (*AN*ti-VEGF antibody for the treatment of predominantly classic *CHOR*oidal neovascularization in age-related macular degeneration),[10,11] have previously demonstrated the efficacy of the monthly dosing regimens of ranibizumab in improving visual acuity (VA) in

ISSN 0161-6420/10/$–see front matter
doi:10.1016/j.ophtha.2010.09.004

patients with subfoveal CNV secondary to age-related macular degeneration (AMD). These studies also described the safety and tolerability profile of intravitreal treatment using ranibizumab. Based on its favorable benefit/risk ratio, ranibizumab received marketing authorization for the treatment of CNV secondary to AMD from the US Food and Drug Administration, the European Medicines Evaluation Agency, and many other national health authorities around the world since 2006.

Although the monthly regimen of ranibizumab provides the best known treatment outcome as indicated by cumulative clinical evidence,[10,11] there was a need to evaluate whether a less frequent treatment regimen can also be effective, while decreasing the treatment burden caused by monthly intravitreal injections. In this context, the PIER (A *P*hase IIIb, Multicenter, Randomized, Double Masked, Sham *I*njection Controlled Study of the *E*fficacy and Safety of *R*anibizumab in Subjects with Subfoveal Choroidal Neovascularization [CNV] with or without Classic CNV Secondary to Age- Related Macular Degeneration) study of the 12-month efficacy of quarterly dosing of ranibizumab after 3 consecutive monthly injections (6 doses per year instead of 12 for the first treatment year) was the first to test an alternative maintenance regimen.[12] The 12-month efficacy result of PIER showed that both 0.3 mg and 0.5 mg ranibizumab injections provided statistically significant superiority in VA improvement as compared with sham treatment, with corresponding treatment differences of ≥3 lines. However, mean changes in best-corrected VA (BCVA) from baseline to month 12 in the quarterly ranibizumab dosing groups (−1.6 letters for 0.3 mg and −0.2 letters for 0.5 mg) was lower than that observed with the monthly dosing regimens of 0.3 mg and 0.5 mg ranibizumab in the MARINA (+7.2 letters) and ANCHOR studies (+11.3 letters). Importantly, because these studies did not directly compare the monthly and quarterly dosing regimens, an appropriate inference of the clinical benefits of the different maintenance treatment regimens is limited.

The first prospective trial designed to directly compare monthly and quarterly ranibizumab dosing regimens, EXCITE evaluated patients with subfoveal CNV secondary to AMD. This 1-year study had an active control arm of continuous monthly injections (0.3 mg) versus the less frequent dosing schedules of 3 initial monthly injections of 0.3 mg or 0.5 mg ranibizumab followed by quarterly injections of the respective doses. The primary objective of this study was to investigate whether a maintenance strategy using a quarterly dosing regimen (0.3 and 0.5 mg) was noninferior to a monthly dosing regimen as determined by the mean change in BCVA from baseline to month 12 in the study population. The key secondary objectives were to assess possible differences in the proportion of patients with loss or gain of BCVA of ≥15 letters, loss of BCVA of ≥30 letters, mean change in central retinal thickness (CRT) from baseline, overall safety, and tolerability.

Methods

Study Design

The EXCITE study was a 1-year, randomized, double-masked, active-controlled, multicenter, Phase IIIb study in patients with subfoveal CNV secondary to AMD, comparing the efficacy and safety of quarterly dosing regimens of ranibizumab with a monthly dosing regimen during the maintenance phase, that is, from month 3 onward.

Eligible patients were randomly assigned in a 1:1:1 ratio to any of the following 3 double-masked treatment arms (Fig 1): loading doses of 3 initial monthly intravitreal injections of 0.3 mg (arm A) or 0.5 mg (arm B) ranibizumab followed by quarterly injections of the respective doses at months 5, 8, and 11 (i.e., a total of 6 injections) or 0.3 mg ranibizumab administered monthly from baseline to month 11 (arm C, active control) (i.e., a total of 12 injections). Primary end point analysis was at month 12. To maintain masking, patients in treatment arms A and B were administered a sham injection during the monthly visits for which no intravitreal injection was scheduled.

This study was conducted in a total of 59 study centers in 16 European countries, Australia, Brazil, Israel, and Turkey in accordance with the declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Approval was obtained from the independent Ethics Committee or Institutional Review board at each participating center. All patients provided signed informed consent before participating in the study. The trial is registered at clinicaltrials.gov (NCT00275821).

Inclusion and Exclusion Criteria

Patients aged ≥50 years and suffering from primary or recurrent subfoveal CNV secondary to AMD, with predominantly classic, minimally classic, or occult (with no classic component) lesions were included in the study. The reading center (DARC) required active CNV for confirmation of the patient inclusion. Other inclusion criteria, based on study eye characteristics were as follows: total area of CNV (including classic and occult components) ≥50% of the total lesion area; the total lesion area ≤12 disc areas for minimally classic or occult with no classic component or ≤9 disc areas (5400 μm) for predominately classic lesions; and BCVA score between 73 and 24 letters (approximately 20/40 to 20/320 Snellen equivalent).

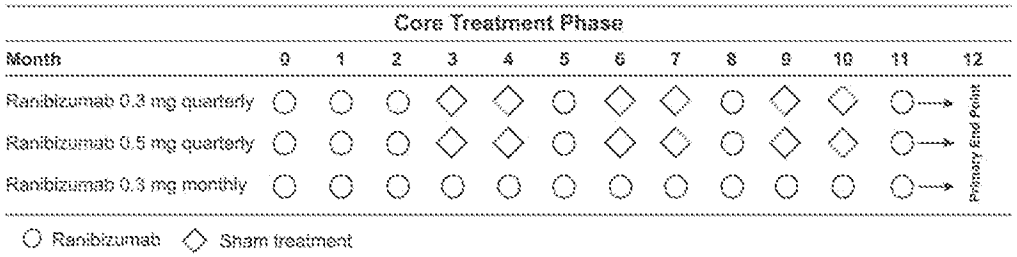


Figure 1. Dosing schedule of ranibizumab regimen in the EXCITE study.

Exclusion criteria were as follows: BCVA score of <34 letters in both eyes; previous treatment or participation in a clinical trial (for either eye) with antiangiogenic drugs; use of any other investigational drugs at the time of screening, or within 30 days or 5 half-lives of screening; prior treatment in the study eye with verteporfin, external-beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy, or transpupillary thermotherapy; operative intervention for AMD in the past in the study eye; laser photocoagulation in the study eye within 1 month preceding baseline; angioid streaks or precursors of CNV in either eye due to other causes; clinically significant subretinal hemorrhage in the study eye that involved the foveal center; or any other significant clinical condition detrimental to the study outcome.

Patients' eligibility was confirmed by an independent masked Central Reading Center, DARC, at screening by fundus photography and fluorescein angiography. The DARC also classified the lesion types and assessed lesion area, area of CNV, and leakage activity based on fluorescein angiography at months 6 and 12. A separate independent masked Central Reading Center (Vienna Reading Center) reviewed optical coherence tomography (OCT) images to provide an objective assessment of retinal thickness for each monthly assessment of all patients.

Study Assessments

Efficacy. Visual acuity was assessed in both eyes at each study visit using Early Treatment Diabetic Retinopathy Study–like charts at an initial testing distance of 4 m. The change in BCVA from baseline to each visit was assessed. The mean change in BCVA from baseline to month 12 was the primary end point. In addition, change in BCVA was assessed as the proportion of patients with <15 letters loss, ≥30 letters loss, ≥0 letters gain, and ≥15 letters gain in BCVA from baseline to month 12. The CRT was measured in both eyes by time domain OCT at screening, and at each monthly visit until month 12. Baseline BCVA and OCT were performed before treatment. Fluorescein angiograms were used to evaluate CNV lesions at screening, month 6, and month 12. In 84% of patients (296 out of 353 patients), visual function contrast sensitivity was assessed in both eyes at baseline, month 6, and month 12 using Pelli-Robson charts.

Safety. Adverse events (AEs), serious AEs, and changes in vital signs were assessed monthly during the study. Biochemical values were measured at screening and at the end of the study visit (month 12), and hematology, blood chemistry, and urine were regularly monitored. Intraocular pressure measurement (before and after each administration by tonometry) and standard ophthalmic examination were also performed monthly.

Statistical Analysis

A population size of 350 randomized patients was planned to reach a sample size of 101 per protocol (PP) patients per treatment arm, assuming a dropout and protocol deviation rate of 13%. The dropout rate and protocol deviation calculations were based on results of the MARINA clinical study data. The PP population was chosen as the primary analysis population to assess the primary end point and to evaluate the null hypothesis of noninferiority of quarterly treatment regimen to monthly treatment regimen in terms of change in BCVA from baseline to month 12. Assuming that there is no difference between quarterly and monthly treatment regimens, there was a power of ≥83% to reject this null hypothesis and therefore conclude that quarterly treatment is noninferior to monthly treatment using 6.8 letters as the noninferiority margin.

For both alternative dosing treatment arms (0.3 and 0.5 mg quarterly), the noninferiority to the reference arm (0.3 mg monthly) was tested using 1-sided testing procedures (or equivalent, using 1-sided confidence intervals [CIs]), while keeping an overall type I error level of 0.025. The Hochberg procedure was used to control for multiplicity; that is, the null hypothesis was rejected if either or both comparisons were statistically significant at a 0.025 level or ≥1 comparison was statistically significant at a 0.0125 level. For both quarterly dosing arms (0.3 and 0.5 mg), the null hypothesis H_0: $u_q - u_m \leq -6.8$ and the alternative hypothesis H_a: $u_q - u_m > -6.8$ were tested, where u_q and u_m were the mean changes in BCVA from baseline/month 3 to month 12 in the quarterly dosing treatment arms (q) and the monthly reference arm (m), respectively, with a noninferiority limit of −6.8. The noninferiority limit was based on the results of a previous study in which the value of 6.8 was approximately one half of the minimum estimated difference (13.6; lower limit of a 2-sided 95% CI) in the mean change in BCVA from baseline to month 12, with testing distance of 4 m between the ranibizumab 0.3 mg and sham injection groups.[9] Noninferiority of 0.5 mg quarterly to 0.3 mg monthly was assessed based on the change from baseline to month 12, and noninferiority analysis of 0.3 mg quarterly versus 0.3 mg monthly could be based on the change from month 3 to month 12 because any differences at month 3 between the 0.3 mg groups could be attributed to chance (up to the month 3 assessment there was no difference in the corresponding treatment regimen).

Table 1. Summary of the EXCITE Patient Disposition

	0.3 mg Quarterly, *n* (%)	0.5 mg Quarterly, *n* (%)	0.3 mg Monthly, *n* (%)	Total, *n* (%)
Enrolled	—	—	—	482
Randomized	120	118	115	353
Completed*	106 (88.3)	95 (80.5)	103 (89.6)	304 (86.1)
Early discontinued from study	14 (11.7)	23 (19.5)	12 (10.4)	49 (13.9)
Adverse event(s)	4 (3.3)	12 (10.2)	5 (4.3)	21 (5.9)
Administrative problems	3 (2.5)	4 (3.4)	4 (3.5)	11 (3.1)
Patient withdrew consent	0	2 (1.7)	1 (0.9)	3 (0.8)
Lost to follow-up	0	1 (0.8)	1 (0.9)	2 (0.6)
Death	0	2 (1.7)	1 (0.9)	3 (0.8)
Abnormal test procedure result(s)	0	0	0	0
Unsatisfactory therapeutic effect	2 (1.7)	1 (0.8)	0	3 (0.8)
Protocol deviation	5 (4.2)	1 (0.8)	0	6 (1.7)

*Completed the study and underwent visual acuity assessment at month 12.

The mean change in BCVA from baseline to month 12 was analyzed by using an analysis of variance with treatment, baseline BCVA (≤52 vs ≥53 letters), and lesion type as factors.

The primary end point was analyzed for both PP and intent-to-treat (ITT) populations. The PP population was a subset of the ITT population and included patients who had an assessment for BCVA at month 12 and with no major study protocol deviation. The ITT population comprised all randomized patients. The last observation carried forward method was used to impute missing values for the ITT population for all efficacy measures. All the safety parameters were calculated for the safety (i.e., ITT, in this study) population.

Results

Patients

A total of 482 patients were screened and 353 patients were randomized for treatment with the study medication. As per the study design, patients received ranibizumab 0.3 mg quarterly (120 patients), ranibizumab 0.5 mg quarterly (118 patients), or ranibizumab 0.3 mg monthly dosing (115 patients). The PP population included 104 patients (86.7%) from the 0.3 mg quarterly, 88 (74.6%) from the 0.5 mg quarterly, and 101 (87.8%) from the 0.3 mg monthly dosing groups. The study was completed by 106 patients (88.3%) in the ranibizumab 0.3 mg quarterly group, 95 (80.5%) in the ranibizumab 0.5 mg quarterly group, and 103 (89.6%) in the ranibizumab 0.3 mg monthly treatment group. In all 3 treatment groups, the most frequently reported reason for early discontinuation from study was AEs (3.3% in 0.3 mg quarterly; 10.2% in 0.5 mg quarterly; 4.3% in 0.3 mg monthly). Details of patient disposition are given in Table 1.

Baseline Characteristics and Treatment Exposure

Baseline demographic and ocular disease characteristics of patients (ITT population) in the EXCITE study are summarized in Table 2. The treatment groups were balanced with respect to baseline BCVA, CRT, and fluorescein angiography of the study eye. Approximately 20% of patients had predominantly classic

Table 2. Demographics and Baseline Characteristics of the Study Eye of Patients who Entered Treatment in the EXCITE Study (Intent-to-Treat Population)

Characteristic	0.3 mg Quarterly (n = 120)	0.5 mg Quarterly (n = 118)	0.3 mg Monthly (n = 115)	Total (n = 353)
Gender, n (%)				
Women	70 (58.3)	73 (61.9)	66 (57.4)	209 (59.2)
Men	50 (41.7)	45 (38.1)	49 (42.6)	144 (40.8)
Race, n (%)				
Caucasian	118 (98.3)	117 (99.2)	113 (98.3)	348 (98.6)
Asian	1 (0.8)	0	0	1 (0.3)
Other	1 (0.8)	1 (0.8)	2 (1.7)	4 (1.1)
Age (yrs)				
Mean (SD)	75.1 (7.45)	75.8 (6.96)	75 (8.26)	75.3 (7.56)
Age group, n (%)				
50–64	13 (10.8)	12 (10.2)	10 (8.7)	35 (9.9)
65–74	37 (30.8)	28 (23.7)	45 (39.1)	110 (31.2)
75–84	61 (50.8)	72 (61.0)	46 (40.0)	179 (50.7)
≥85	9 (7.5)	6 (5.1)	14 (12.2)	29 (8.2)
History				
Years since first diagnosis, mean (SD)	0.57 (1.424)	0.52 (1.14)	0.56 (2.177)	0.55 (1.629)
BCVA (letters)*				
Mean (SD)	55.8 (11.81)	57.7 (13.06)	56.5 (12.19)	56.7 (12.4)
≤52	46 (38.3)	33 (28.0)	36 (31.3)	115 (32.6)
≥53	74 (61.7)	85 (72.0)	79 (68.7)	238 (67.4)
BCVA (Snellen equivalent)*				
≤20/200	5 (4.2)	8 (6.8)	6 (5.2)	19 (5.4)
>20/200 and <20/40	94 (78.3)	84 (71.2)	86 (74.8)	264 (74.8)
≤20/40	21 (17.5)	26 (22.0)	23 (20.0)	70 (19.8)
CNV classification				
Predominantly classic	25 (20.8)	27 (22.9)	21 (18.3)	73 (20.7)
Minimally classic	50 (41.7)	46 (39.0)	46 (40.0)	142 (40.2)
Occult (no classic)	45 (37.5)	45 (38.1)	48 (41.7)	138 (39.1)
Retinal thickness at central point (μm)§				
n	100	100	95	295
Mean (SD)	313.6 (85.05)	324.5 (115.94)	320.6 (118.55)	319.5 (107.13)
Retinal thickness at central subfield (μm)				
Mean (SD)	321.4 (86.80)	331.9 (105.74)	326.6 (99.44)	326.6 (97.38)

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
*Measured using ETDRS-like charts at a distance of 4 m.
§Measured using optical coherence tomography.

lesion, 40% patients had minimally classic lesion, and 40% patients had occult (with no classic component) lesion.

The mean (standard deviation) number of active treatment injections received over the study treatment period from baseline to month 11 were 5.7 (0.80), 5.5 (1.05), and 11.4 (1.69) in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively.

Efficacy

The mean change in BCVA in the study eye from baseline over time (PP population) is shown in Figure 2A. In the PP population, the mean BCVA increase from baseline to month 12 (primary end point) was 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively. In all the 3 treatment arms, the mean BCVA increased from baseline to month 3 (monthly dosing phase for all treatment arms) by 6.8, 6.6, and 7.5 letters, in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively. However, between months 3 and 12 (maintenance phase), patients in the quarterly treatment groups lost 1.8 (0.3 mg quarterly) and 2.8 (0.5 mg quarterly) letters, whereas patients in the monthly treatment group gained 0.8 letters on average. Up to month 3, there was no notable difference between the treatment arms. The first notable difference was observed at month 4, that is, 2 months after the last loading dose (Fig 2A). Although this study was designed to test noninferiority of the quarterly treatment regimen versus monthly treatment regimen, this was not achieved for the 0.5 mg quarterly regimen, as evidenced by the lower CI limits for the corresponding treatment difference being below the noninferiority threshold of −6.8 letters (95% CI, −7.9 to −0.7; 97.5% CI, −8.4 to −0.2; $P = 0.0867$). For the comparison of 0.3 mg quarterly versus 0.3 mg monthly treatment groups (from months 3 to 12), the lower CI limit (97.5% CI, −5.6 to 0.22; $P = 0.0008$), however, indicates a theoretical noninferiority, also driven by the smaller variability in the end point 'change from months 3 to 12' compared with 'change from baseline to month 12.' However, given that the 97.5% CI barely includes 0, it can be interpreted that 0.3 mg quarterly treatment is numerically inferior to the 0.3 mg monthly treatment regimen.

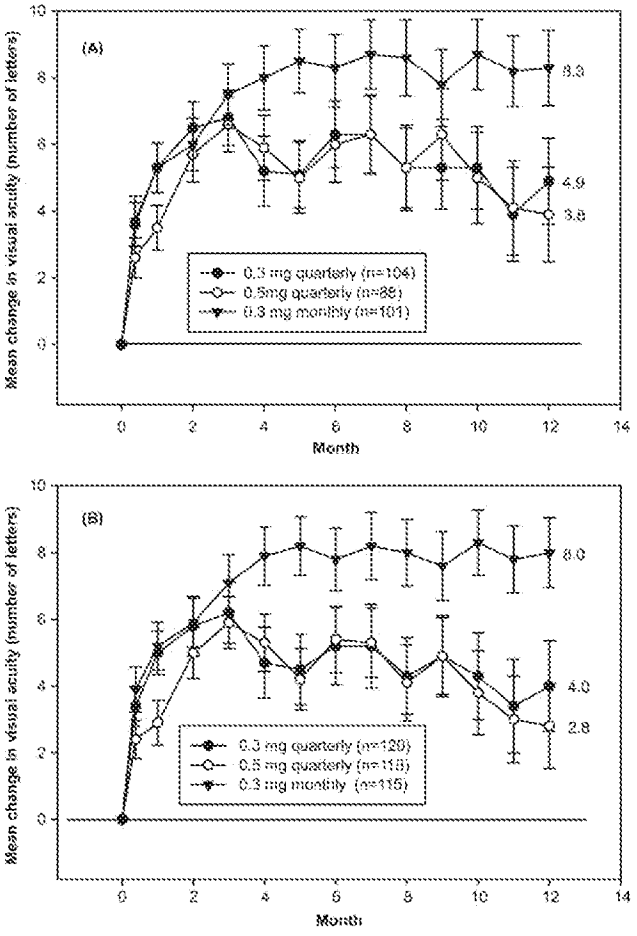


Figure 2. Mean change in best-corrected visual acuity score from baseline over time in the (A) per-protocol population (study visit) and (B) intent-to-treat population (last observation carried forward [LOCF]) of EXCITE. Vertical bars represent standard error of the mean.

The BCVA time course in the ITT population (last observation carried forward method) was consistent with that of the PP population, with a mean change in BCVA from baseline to month 12 of 4.0, 2.8, and 8.0 letters for the ranibizumab 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively ($P = 0.0751$ [95% CI, −7.7 to −0.9] for the 0.3 mg quarterly and $P = 0.1678$ [95% CI, −8.6 to −1.7] for the 0.5 mg quarterly, both compared with the 0.3 mg monthly group). In the monthly treatment regimen, the initially gained mean BCVA remained stable during the treatment period, whereas it gradually decreased in the quarterly treatment regimens with a pattern reflecting the impact of the quarterly injections (Fig 2B). The BCVA values at baseline and the change from baseline at month 12 are given in Table 3 for both the PP and the ITT populations.

The proportion of patients who lost <15 letters from baseline to month 12 was similar across the treatment groups (ITT population) with 93.3%, 91.5%, and 94.8% in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly ranibizumab groups, respectively (Fig 3A). The proportion of patients who had a VA gain of ≥15 letters from baseline to month 12 was 14.2% in the ranibizumab 0.3 mg quarterly group, 17.8% in the ranibizumab 0.5 mg quarterly group, and 28.7% in the ranibizumab 0.3 mg monthly group (Fig 3B). The proportion of patients with a gain of ≥0 letters of VA were 71.7% (86/120; 0.3 mg quarterly), 66.9% (79/118; 0.5 mg quarterly), and 82.6% (95/115; 0.3 mg monthly) at month 12.

The percentage of patients, at month 12, with a VA Snellen equivalent of ≤20/200 (BCVA = 34 letters) was greater in the quarterly dosing regimen (7.5% for 0.3 mg and 6.8% for 0.5 mg) compared with the 0.3 mg monthly dosing regimen (2.6%). Severe vision loss (≥30 letters) at the end of this study was observed in 2 patients (1.7%) of each of the quarterly treatment groups and in none of the 0.3 mg monthly treatment group.

Anatomically, the overall reduction in CRT of the study eye from baseline to month 3 and to month 12 was similar between the 3 treatment groups in the ITT population. However, although the mean CRT decreased similarly from baseline to month 3 in all 3 treatment groups, thereafter it remained more or less stable at the monthly dosing regimen but was variable in the quarterly dosing groups (mean CRT decrease 1 month after each treatment and increase thereafter until next treatment visit at months 5, 8, and 11; Fig 4). The mean change in CRT from baseline to month 12 was similar between the 0.5 mg quarterly group (−105.6 μm) and the 0.3 mg monthly group (−105.3 μm). For the 0.3 mg quarterly group, the mean CRT change was −96.0 μm. The overall retinal thickness at the central subfield of the study eye at baseline and months 3 and 12 was also similar between the treatment groups.

On the basis of angiographic data, the mean decrease in CNV lesion area from baseline to month 12 was numerically higher in the 0.5 mg quarterly treatment group compared with the other treatment groups; however, this difference was not significant (−2.28 mm^2 in the 0.3 mg quarterly, −3.49 mm^2 in the 0.5 mg

Table 3. Best-Corrected Visual Acuity at Baseline and Mean Change from the Baseline in the Study Eye at Month 12

	0.3 mg Quarterly	0.5 mg Quarterly	0.3 mg Monthly
PP population (observed)			
n	104	88	101
Baseline mean (SD)	55.3 (12.11)	57.5 (13.07)	56.2 (12.33)
Month 12 mean (SD)	60.2 (16.01)	61.3 (16.32)	64.5 (16.27)
Change from baseline, mean (SD)	4.9 (13.13)	3.8 (13.33)	8.3 (11.31)
Comparison vs monthly dosing			
Mean difference (SE)	−3.3 (1.76)	−4.5 (1.84)	
95% CI	−7.1, −0.2	−7.9, −0.7	
97.5% CI[§]	−7.6, 0.3	−8.4, −0.2	
P-value*[§]	0.0365	0.0867	
ITT population (LOCF)			
n	120	118	115
Baseline mean (SD)	55.8 (11.81)	57.7 (13.06)	56.5 (912.19)
Month 12 mean	59.8 (17.20)	60.5 (16.50)	64.5 (15.85)
Change from baseline, mean (SD)	4.0 (14.88)	2.8 (13.78)	8.0 (11.27)
Comparison vs monthly dosing			
Mean difference (SE)	−3.9 (1.75)	−5.2 (1.76)	
95% CI	−7.7, −0.9	−8.6, −1.7	
97.5% CI	−8.2, −0.4	−9.1, −1.2	
P-value*	0.0751	0.1678	

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; PP = per protocol; SD = standard deviation; SE = standard error.
*One-sided test of H_0: mean difference(test-reference) ≤ -6.8.
[§]The CI for the difference between months 3 and 12 (0.3 mg quarterly group) is −5.6, 0.22 ($P = 0.0008$).

quarterly, and −2.63 mm^2 in the 0.3 mg monthly dosing regimen; Table 4). The mean change (decrease) from baseline to month 12 in the total area of leakage and total lesion area are shown in Table 4.

Contrast sensitivity analysis (ITT population; last observation carried forward method) at month 6 showed a mean change of 0.071 log units from baseline in the 0.3 mg quarterly group (100 patients), 0.107 log units in the 0.5 mg group quarterly group (98 patients), and 0.123 log units in the 0.3 mg monthly treatment group (98 patients). In the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly treatment groups, the mean change from baseline to month 12 showed an overall improvement by 0.085, 0.081, and 0.131 log units, respectively.

Safety

The AEs (≥3% in any group) are summarized in Table 5 (available online at http://aaojournal.org). The most frequently reported ocular AEs were eye pain (18.3%, 11.9%, and 20.9% in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively), conjunctival hemorrhage (19.2 %, 16.1%, and 10.4% in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively), reduced VA (13.3%, 16.1%, and 7.8% in the 0.3 mg quarterly, 0.5 mg monthly, and 0.3 mg monthly groups, respectively), and increased intraocular pressure of >10 mmHg (5.0%, 5.9%, and 14.8% in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively). Among the nonocular AEs reported, the incidence of nasopharyngitis was the highest (9.2%, 3.4%, and 7.0% in the 0.3 mg quarterly, 0.5 mg quarterly, and 0.3 mg monthly groups, respectively), followed by hypertension (8.3% for 0.3 mg quarterly, 5.1% for 0.5 mg quarterly, and 7.0% for 0.3 mg monthly). There was no apparent trend of a dose or treatment frequency–related change in AE incidences, although differences between groups were observed with respect to individual AEs.

A total of 12 patients (10.0%) in the 0.3 mg quarterly group, 10 patients (8.5%) in the 0.5 mg quarterly group, and 13 patients (11.3%) in the monthly treatment group experienced AEs that could be potentially related to systemic VEGF inhibition (Table 6; available online at http://aaojournal.org). Arteriothromboembolic events reported in this study showed no increased risk of stroke in the monthly dosing regimen as compared with that of the quarterly dosing regimens (Table 6). There were 3 incidences of angina pectoris (1 in each of the groups) and 2 incidences of myocardial infarction (1 each in 0.3 mg quarterly and monthly groups). Other incidences of arteriothromboembolic events were cerebrovascular accident (1 in 0.3 mg monthly group) and pulmonary embolism (1 in the 0.3 mg monthly group). Nonocular hemorrhage was reported in the 0.5 mg quarterly group (4 patients; 3.4%) and in the 0.3 mg monthly group (1 patient; 0.9%).

Incidences of serious AEs were reported in 15 patients (12.5%) in the ranibizumab 0.3 mg quarterly group, 23 patients (19.5%) in the 0.5 mg quarterly group, and 20 patients (17.4%) in the 0.3 mg monthly treatment group (Table 7; available online at http://aaojournal.org). The incidence of ocular serious AEs in the study eye was low: 2.5% in the 0.3 mg quarterly group, 4.2% in the 0.5 mg quarterly group, and 0.9% in the 0.3 mg monthly group. Three deaths occurred during this study (Table 7), which were due to cardiorespiratory arrest and cerebral hemorrhage (both in the 0.5 mg quarterly group) and lung infection (1 in the 0.3 mg monthly group). Of the 3 deaths, 1 was suspected to be related to the study medication. This patient (male, 73 years) received treatment of 0.5 mg ranibizumab quarterly and had an active medical condition, including diabetes mellitus, hypertension, chronic renal failure, drug hypersensitivity, cataract in both eyes, dementia Alzheimer's type, gastritis, vitamin B complex deficiency, hypercholesterolemia, and hyperuricemia, and was under multiple concomitant medications. The patient died owing to cerebral hemorrhage 41 days after the previous ranibizumab administration.

Study discontinuation owing to AEs was higher in the 0.5 mg quarterly group (13 patients, 11%), compared with the 0.3 mg quarterly (4 patients, 3.3%) or the 0.3 mg monthly treatment group

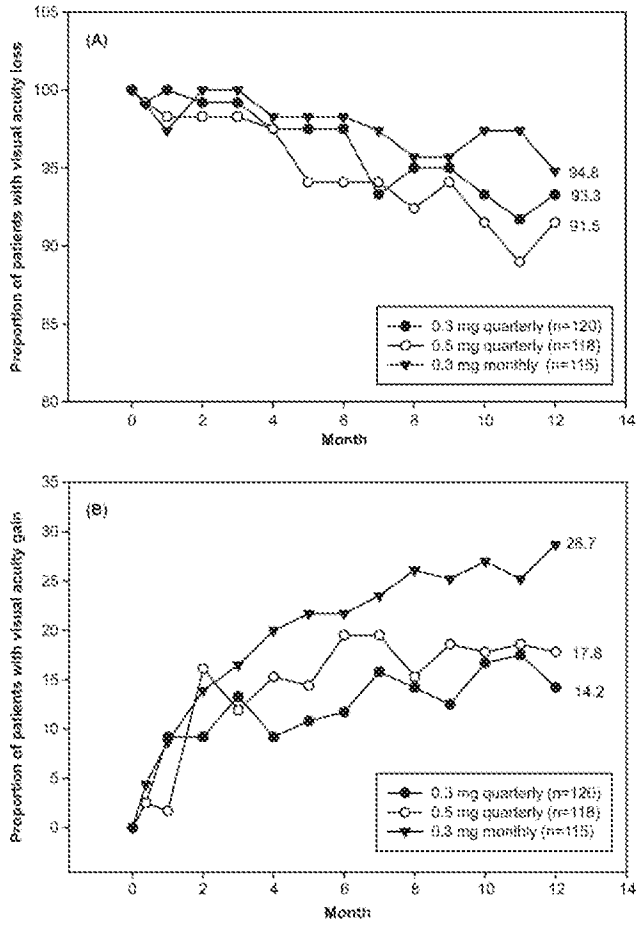


Figure 3. Proportion of patients with (A) visual acuity loss (<15 letters) or (B) gain (≥15 letters) over time in the intent-to-treat patient population (last observation carried forward [LOCF]) of EXCITE.

(6 patients, 5.2%). Ocular AEs of the study eye that led to treatment discontinuation were reported in 3 patients (2.5%) in the 0.3 mg quarterly group, 5 patients (4.2%) in the 0.5 mg quarterly group, and 1 patient (0.9%) in the 0.3 mg monthly treatment group. Two patients (1.7%) from the 0.5 mg quarterly group discontinued because of AEs of the fellow eye.

Discussion

The EXCITE trial is the first study directly comparing visual outcomes between monthly and quarterly dosing regimens in the treatment of patients with subfoveal CNV, secondary to AMD. The EXCITE study offers a rigorous analysis of the quarterly treatment regimen, with monthly study visits and OCT assessments, providing a monthly monitoring of functional and anatomic changes in the study eye. The EXCITE study allows to (1) compare the study outcome under monthly vs. quarterly treatment and (2) assess the anatomic and functional changes at a monthly interval (i.e., also at visits without treatment).

This study was designed to show noninferiority of the quarterly treatment regimen compared with a monthly treatment regimen, which was not achieved according to the currently accepted margin of ≤5.0 letters. The drop in BCVA in the quarterly treatment regimen during the time points wherein the treatment was skipped suggests an overall superiority of the monthly treatment regimen. The efficacy shown in the monthly treatment group, in this study, was consistent with that of previous ranibizumab Phase III trials[9–11] using an exclusive monthly retreatment strategy. The primary efficacy variable (BCVA) was consistent between the PP population (no major protocol violation) and the ITT population. The improvement in BCVA obtained in the ITT population (including all lesion types) receiving the 0.3 mg monthly dosing regimen (8.0 letters) is in line with that of the ANCHOR (8.5 letters, 0.3 mg; 11.3 letters, 0.5 mg)[10] and MARINA (6.5 letters, 0.3 mg; 7.2, 0.5 mg)[9] trials. Also, the other VA outcomes in this group, such as the proportion of patients with loss or gain of BCVA (15 letters) and BCVA equaling ≤34 letters, are similar to those of the ANCHOR study and better than those of the MARINA study. A comparison of the quarterly results from this study to the pivotal PIER study[12] revealed numerically better BCVA improvement in EXCITE patients. The PIER study compared the efficacy of quarterly dosing of ranibizumab with that of sham treatment. The mean BCVA increased from baseline to month 12 for the quarterly dosing groups in EXCITE by 4.0 letters in the 0.3 mg quarterly group and 2.8 letters in the 0.5 mg group, whereas in the PIER study, although superior to sham treatment, the BCVA dropped over the 12-month study period to −1.6 letters in 0.3 mg quarterly and −0.2 letters in the 0.5 mg quarterly groups. The efficacy results from the EXCITE study demonstrate that on average and in contrast with the monthly treatment group a quarterly ranibizumab treatment regimen is not able to maintain the initially gained BCVA. In this study, although noninferiority was not achieved for the quarterly treatment regimen in terms of BCVA improvement to levels seen for the monthly treatment, there were also patients who maintained the BCVA improvement (i.e., after the initial 3 monthly dosing) in the quarterly treatment

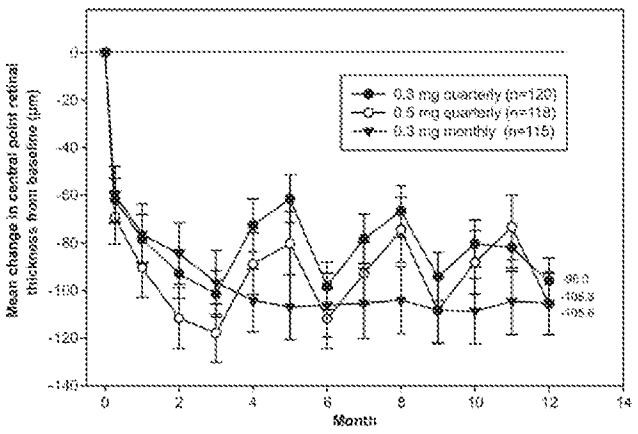


Figure 4. Mean change from baseline over time of central retinal thickness as assessed by optical coherence tomography scan in the intent-to-treat patient population (last observation carried forward [LOCF]) of EXCITE. Vertical bars represent standard error of the mean.

Table 4. Mean Change from Baseline of the Total Area (mm^2) of Choroidal Neovascularization in the Study Eye and Total Area of Leakage in the EXCITE Study (Intent-to-Treat Population, Last Observation Carried Forward)

	0.3 mg Quarterly	0.5 mg Quarterly	0.3 mg Monthly
n†	113	105	108
Total area of CNV			
Baseline, mean (SD)	7.99 (5.161)	9.23 (5.644)	9.03 (5.539)
Month 12, mean (SD)	5.70 (6.997)	5.74 (5.843)	6.40 (6.840)
Change from baseline, mean (SD)	−2.28 (5.859)	−3.49 (5.962)	−2.63 (6.136)
Comparison vs monthly dosing			
Mean difference (SE)	0.35 (0.805)	−0.85 (0.820)	
95% CI	(−1.40, 1.56)	(−2.27, 0.74)	
P-value*	0.9147	0.3179	
Area of leakage			
Baseline mean (SD)	8.57 (4.981)	9.85 (5.280)	9.67 (5.407)
Month 12, mean (SD)	5.77 (6.979)	5.76 (5.875)	6.34 (6.883)
Mean change (SD)	−2.80 (5.970)	−4.09 (6.026)	−3.33 (6.400)
Comparison vs monthly dosing			
Mean difference (SE)	0.52 (0.825)	−0.76 (0.841)	
95% CI	(−1.26, 1.75)	(−2.13, 0.92)	
P-value*	0.7534	0.4365	

CI = confidence interval; CNV = choroidal neovascularization; SD = standard deviation; SE = standard error.
†Patients with both a baseline and postbaseline value at the specific visit.
*Two-sided test of H_0: mean difference (test − reference) = 0.

regimen. An earlier report on subgroup analysis of the patient population in the EXCITE study showed that the quarterly treatment maintained BCVA in 41.6% patients (Eldem B, Bartz-Schmidt K-U, Schlingemann RO, et al; Association for Research in Vision and Ophthalmology 2009 Annual Meeting, 3–7 May 2009, Fort Lauderdale, FL).

With respect to morphologic effects, the monthly dosing group showed an initial improvement followed by maintenance of the improved CRT thereafter; however, the quarterly dosing regimens showed intermittent retinal thickening between the retreatment intervals. The increase in mean BCVA and decrease in mean CRT, particularly during the initial study treatment period, suggest a temporal association between the functional and morphologic changes related to study treatment. This association is also reflected by the quarterly decrease in vision gain and the quarterly increase in CRT before ranibizumab injection in the quarterly treatment groups during the maintenance phase. This fluctuation indicates that patients on average could not be stabilized with respect to visual function or retinal morphology using the tested quarterly treatment regimens. The time of dissociation between responses in the monthly and quarterly regimes starts between months 3 and 4, that is, as soon as there is a difference in the regimens; therefore, this may be considered an adequate interval to analyze the efficacy of treatment. It is at month 4 when the first notable difference between the quarterly and monthly regimens becomes evident.

The AEs observed in the study were comparable between the groups, and no new safety concerns were noted. The most frequently reported ocular AE was eye pain. For the most frequently reported nonocular AEs (nasopharyngitis and hypertension), there seems to be no indication of a difference between the monthly and quarterly dosing regimens. The incidence of key arteriothromboembolic events was also low in this study, although the actual number of patients experiencing an event in the 0.3 mg monthly dosing regimen was higher (3.5%) compared with 1.7% in the 0.3 mg quarterly and 0.8% in the 0.5 mg quarterly treatment groups. The overall safety results from the EXCITE study are consistent with those reported in the previous trials[9–12] and confirm the robust safety profile of ranibizumab.

In conclusion, after 3 initial monthly ranibizumab injections, both monthly (0.3 mg) and quarterly (0.3 mg/0.5 mg) ranibizumab treatments maintained BCVA in patients with CNV secondary to AMD during the 12-month treatment. At month 12, the gain in BCVA observed in the monthly regimen was higher than that of the quarterly regimens. Noninferiority of quarterly regimen was not achieved with reference to the currently accepted margin of 5.0 letters, indicating clinical superiority of the monthly treatment regimen. Both monthly and quarterly dosing regimens were well tolerated. The direct comparative analysis between monthly and quarterly treatment regimens of the EXCITE study is consistent with the clinical guidance on ranibizumab treatment,[13] which recommends rigorous monthly monitoring with timely retreatment of patients with recurrent disease activity to achieve the best treatment outcomes for patients.

Acknowledgments. The authors acknowledge medical writing assistance from Ajithkumar Vasudevan, PhD, and Shivani Mittra, PhD, Novartis Healthcare Pvt Ltd.

References

1. Keyt BA, Berleau LT, Nguyen HV, et al. The carboxyl-terminal domain (111-165) of vascular endothelial growth factor is critical for its mitogenic potency. J Biol Chem 1996; 271:7788–95.

2. Ferrara N, Mass RD, Campa C, Kim R. Targeting VEGF-A to treat cancer and age-related macular degeneration. Annu Rev Med 2007;58:491–504.
3. Penn JS, Madan A, Caldwell RB, et al. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 2008;27: 331–71.
4. Waisbourd M, Loewenstein A, Goldstein M, Leibovitch I. Targeting vascular endothelial growth factor: a promising strategy for treating age-related macular degeneration. Drugs Aging 2007;24:643–62.
5. Grisanti S, Tatar O. The role of vascular endothelial growth factor and other endogenous interplayers in age-related macular degeneration. Prog Retin Eye Res 2008;27:372–90.
6. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26:859–70.
7. Lowe J, Araujo J, Yang J, et al. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. Exp Eye Res 2007;85:425–30.
8. Chen Y, Wiesmann C, Fuh G, et al. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. J Mol Biol 1999;293:865–81.
9. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
10. Brown DM, Kaiser PK, Michels M, et al, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355: 1432–44.
11. Brown DM, Michels M, Kaiser PK, et al, ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology 2009;116: 57–65.
12. Regillo CD, Brown DM, Abraham P, et al, PIER Study Group. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–48.
13. Mitchell P, Korobelnik JF, Lanzetta P, et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol 2010;94:2–13.

Footnotes and Financial Disclosures

Originally received: December 19, 2009.
Final revision: September 6, 2010.
Accepted: September 8, 2010.
Available online: ●●●. Manuscript no. 2009-1732.

[1] Department of Ophthalmology, University of Vienna, Waehringer Guertel, Vienna, Austria.

[2] Hacettepe University Faculty of Medicine, Sihhiye, Ankara, Turkey.

[3] Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia.

[4] Hôpital Pellegrin, Bordeaux Cedex, France.

[5] Academisch Medisch Centrum Universiteit van Amsterdam, Amsterdam, The Netherlands.

[6] Rabin Medical Center, Beilinson Campus, Petach-Tikva, Israel.

[7] University Leipzig, Klinik und Poliklinik für Augenheilkunde, Leipzig, Germany.

[8] Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

[9] Novartis Pharma AG, Basel, Switzerland.

*A list of the primary investigators for the EXCITE study is available at http://aaojournal.org.

Presented at: EURETINA, May 14–17, 2009, Nice, France, and ARVO, May 3–7, 2009, Fort Lauderdale, Florida.

Financial Disclosure(s):
The authors have made the following disclosures:
Ursula Schmidt-Erfurth – Consultant – Alcon Laboratories Inc., Bayer Healthcare, Carl Zeiss Meditec, Heidelberg Engineering Inc., Novartis Pharmaceutical Corporation, Regeneron; Research Grant – Bayer Healthcare, Carl Zeiss Meditec, Novartis Pharmaceutical Corporation
Bora Eldem – Lecture Fee, Financial Support for this project – Novartis Pharmaceuticals Corporation
Robyn Guymer – Consultant – Novartis Pharmaceuticals Corporation
Jean-Francois Korobelnik – Consultant –Alcon Laboratories, Bayer Healthcare, Novartis Pharmaceuticals Corporation, THEA
Reinier Schlingemann – Consultant, Lecture Fee – Novartis Pharmaceuticals Corporation
Peter Wiedemann – Lecture Fee – Novartis Pharmaceutical Corporation
Christian Simader – Consultant – Novartis Pharmaceutical Corporation
Margarita Gekkieva –Employee – Novartis Pharma
Andreas Weichselberger –Employee – Novartis Pharma
Supported by Novartis Pharma, AG, Switzerland.

Correspondence:
Ursula Schmidt-Erfurth, Department of Ophthalmology, University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. E-mail: ursula.schmidt-erfurth@meduniwien.ac.at.

Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema

The RESTORE Extension Study

*Ursula Schmidt-Erfurth, MD,[1] Gabriele E. Lang, MD,[2] Frank G. Holz, MD,[3] Reinier O. Schlingemann, MD,[4,5] Paolo Lanzetta, MD,[6,7] Pascale Massin, MD, PhD,[8] Ortrud Gerstner, MSc,[9] Abdelkader Si Bouazza,[9] Haige Shen, PhD,[10] Aaron Osborne, MD,[9] Paul Mitchell, MD, PhD,[11] on behalf of the RESTORE Extension Study Group**

Objective: To evaluate long-term efficacy and safety profiles during 3 years of individualized ranibizumab treatment in patients with visual impairment due to diabetic macular edema (DME).

Design: Phase IIIb, multicenter, 12-month, randomized core study and 24-month open-label extension study.

Participants: Of the 303 patients who completed the randomized RESTORE 12-month core study, 240 entered the extension study.

Methods: In the extension study, patients were eligible to receive individualized ranibizumab treatment as of month 12 guided by best-corrected visual acuity (BCVA) and disease progression criteria at the investigators' discretion. Concomitant laser treatment was allowed according to the Early Treatment Diabetic Retinopathy Study guidelines. Based on the treatments received in the core study, the extension study groups were referred to as prior ranibizumab, prior ranibizumab + laser, and laser.

Main Outcome Measures: Change in BCVA and incidence of ocular and nonocular adverse events (AEs) over 3 years.

Results: Overall, 208 patients (86.7%) completed the extension study. In patients treated with ranibizumab during the core study, consecutive individualized ranibizumab treatment during the extension study led to an overall maintenance of BCVA and central retinal subfield thickness (CRST) observed at month 12 over the 2-year extension study (+8.0 letters, −142.1 μm [prior ranibizumab] and +6.7 letters, −145.9 μm [prior ranibizumab + laser] from baseline at month 36) with a median of 6.0 injections (mean, 6.8 injections; prior ranibizumab) and 4.0 (mean, 6.0 injections; prior ranibizumab + laser). In the prior laser group, a progressive BCVA improvement (+6.0 letters) and CRST reduction (−142.7 μm) at month 36 were observed after allowing ranibizumab during the extension study, with a median of 4.0 injections (mean, 6.5 injections) from months 12 to 35. Patients in all 3 treatment groups received a mean of <3 injections in the final year. No cases of endophthalmitis, retinal tear, or retinal detachment were reported. The most frequently reported ocular and nonocular adverse effects over 3 years were cataract (16.3%) and nasopharyngitis (23.3%). Eight deaths were reported during the extension study, but none were suspected to be related to the study drug/procedure.

Conclusions: Ranibizumab was effective in improving and maintaining BCVA and CRST outcomes with a progressively declining number of injections over 3 years of individualized dosing. Ranibizumab was generally well tolerated with no new safety concerns over 3 years. *Ophthalmology 2014;121:1045-1053 © 2014 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).*

*Supplemental material is available at www.aaojournal.org.

Diabetic macular edema (DME) is one of the leading causes of visual impairment in the working-age population in developed countries.[1] In addition to DME, patients with diabetes also are prone to multiple systemic comorbidities.[2] For this large population with chronic disease requiring extended lifelong therapy in a challenging environment, it is particularly important to identify manageable DME treatment strategies that provide long-term safety and efficacy profiles. Although focal/grid laser photocoagulation is an established treatment option for patients with visual impairment due to DME and is known to stabilize vision, it does not appear to be effective in improving vision in the majority of patients.[3] Thus, there is a need for treatments that are safe and manageable and that can improve vision in patients with DME. Ranibizumab is a

http://dx.doi.org/10.1016/j.ophtha.2013.11.041
ISSN 0161-6420/14

humanized monoclonal antibody fragment (Fab) specifically designed for ocular use. It binds to vascular endothelial growth factor (VEGF)-A with high affinity, inhibits multiple isoforms of VEGF-A, and has minimal systemic exposure after intravitreal injection.[4] Ranibizumab (Lucentis; Novartis, Basel, Switzerland and Genentech Inc., South San Francisco, CA) is approved in many countries for 4 major indications: neovascular age-related macular degeneration, visual impairment due to DME, visual impairment secondary to macular edema in branch or central retinal vein occlusion, and visual impairment due to choroidal neovascularization secondary to pathologic myopia.[5]

Several studies with different dosing regimens and treatment algorithms have established the efficacy and safety profiles of ranibizumab treatment in patients with DME. Long-term data recently became available, allowing the evaluation of continued therapy effects and recognizing patterns of chronic disease activity. The Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RISE [N = 377] and RIDE [N = 382]) studies demonstrated that monthly ranibizumab treatment over 24 months was well tolerated and associated with superior best-corrected visual acuity (BCVA) outcomes compared with monthly sham injections.[6] Two-year results of the Diabetic Retinopathy Clinical Research Network (DRCR.net; N = 691) and Ranibizumab for Edema of the mAcula in Diabetes (READ-2; N = 126) studies demonstrated that ranibizumab alone or in combination with laser (prompt/deferred) provided superior and sustained BCVA gains compared with laser photocoagulation monotherapy using an individualized dosing algorithm.[7,8] Of note, the 3-year results of the DRCR.net study reported complete BCVA maintenance from year 2 to year 3 with only 1 to 2 (median) injections in year 3.[9] The DRCR.net study also permitted less frequent than monthly follow-up for patients with stable absence of macular edema. The median number of clinic visits in the third year of the DRCR.net study was 7 to 8.[9] The 3-year outcomes of the READ-2 study suggested that aggressive retreatment as per individual patient needs based on continued or recurrent activity defined by intraretinal fluid at the central macula resulted in BCVA improvement and reduction in central retinal subfield thickness (CRST).[10] In contrast to these studies, in the RESTORE study ranibizumab treatment was administered using an individualized dosing regimen based on BCVA stability and disease progression criteria, in line with the current ranibizumab label in European Union (EU).[3] The RESTORE study aims to address the need to optimally manage patients with diabetes by assessing the long-term safety and efficacy profiles and the re-treatment needs for ranibizumab.

The RESTORE core study (registered as NCT00687804 at http://clinicaltrials.gov/; accessed June 25, 2013) demonstrated that ranibizumab alone or combined with laser provided superior visual acuity (VA) gains when compared with laser monotherapy in patients with visual impairment due to DME over 12 months.[11] Similar to the core study, in the RESTORE extension study, ranibizumab was administered according to an individualized dosing regimen based on the investigators' discretion; treatment was guided by BCVA stability and disease progression criteria, with monthly monitoring. All patients who completed the core study were eligible to receive ranibizumab treatment during the extension study. The first year interim results of this extension study demonstrated that ranibizumab treatment was well tolerated and no new ocular or nonocular safety concerns were observed over 2 years. Furthermore, the individualized dosing regimen was successful in maintaining (prior ranibizumab groups) and improving (prior laser group) the BCVA gains observed at the end of the core study over the first year of the extension study.[12]

The consecutive analysis presented in this article describes the extended efficacy and safety findings of individualized ranibizumab 0.5 mg treatment based on the complete 3-year data of the RESTORE core and extension studies conducted in patients with visual impairment due to DME.

Methods

Study Design

The RESTORE extension study was a phase IIIb, 24-month, open-label, multicenter study (month 12 to month 36) conducted in patients with DME who completed the 12-month RESTORE core study (day 1 to month 12; Fig 1, available at www.aaojournal.org). In the RESTORE core study, patients were randomized to receive ranibizumab, ranibizumab + laser, or laser alone. In the extension study, all patients could receive individualized ranibizumab treatment according to the prespecified stability-based BCVA and the disease progression re-treatment criteria. During the extension study, the investigators remained masked to the treatment administered during the core study. All patients were eligible to receive laser pro re nata (PRN) in accordance with Early Treatment Diabetic Retinopathy Study (ETDRS) guidelines at the investigators' discretion. The study was conducted in accordance with the Declaration of Helsinki, and every patient provided new written informed consent before entering the extension study. The study is registered with clinicaltrials.gov (accessed June 25, 2013; NCT00906464).

Patients

The RESTORE core study enrolled 345 patients aged ≥18 years with type 1 or 2 diabetes mellitus (per American Diabetes Association or World Health Organization guidelines), hemoglobin (Hb) A1c ≤10%, and visual impairment due to DME with a BCVA letter score between 78 and 39 letters, based on ETDRS-like VA testing charts at a testing distance of 4 m (approximate Snellen equivalent 20/32−20/160).

Patients who completed the randomized 12-month RESTORE core study assessments and provided new written informed consents for the extension were included in the RESTORE extension study. Key exclusion criteria for the extension study were history of stroke or transient ischemic attack; hypersensitivity to ranibizumab or any component of the ranibizumab formulation; uncontrolled glaucoma in either eye (intraocular pressure [IOP] >24 mmHg with medication or according to investigator's judgment); evidence of vitreomacular traction (in either eye) or active proliferative diabetic retinopathy (study eye); use of other investigational drugs at the time of enrollment or within 30 days or 5 half-lives before enrollment, whichever was longer; and ocular conditions in the study eye that required chronic concomitant therapy with topical ocular corticosteroids.

Objectives

The primary objective of the RESTORE extension study was to evaluate the safety profile of ranibizumab 0.5 mg on the basis of

the incidences of ocular and nonocular adverse events (AEs) during the 24-month extension study period (i.e., months 12–36). Secondary objectives were to describe the ocular and nonocular AEs over 36 months (i.e., day 1 to month 36) in patients treated with ranibizumab 0.5 mg and to evaluate the change in BCVA from core baseline over 24 months of the extension study (i.e., months 12–36) and over 36 months of the entire study period.

Treatment

The RESTORE extension was an open-label study. All patients enrolled in the extension study were eligible to receive intravitreal ranibizumab 0.5 mg injections on the basis of the prespecified retreatment criteria, and monthly visits were mandated for each patient.

Ranibizumab 0.5 mg was administered as an intravitreal injection under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum. Patients were treated at monthly intervals until stable vision was achieved, that is, no further BCVA improvement attributable to treatment was observed compared with the 2 previous consecutive visits according to the investigator or a BCVA letter score of ≥84 letters (approximate Snellen equivalent of 20/20) was observed. If, on the basis of the investigators' opinion, a decrease in BCVA due to DME was observed, monthly ranibizumab treatment was resumed until stable BCVA was reached. Ranibizumab injection at the baseline of the extension study (i.e., month 12) was not mandated, and a maximum of 24 monthly ranibizumab injections could be administered during the extension study (months 12–35). Also, patients previously treated with laser monotherapy who entered the extension study did not mandatorily receive the 3 initial injections that were administered to patients in the ranibizumab groups at the beginning of the core study. During the 2-year extension study, all patients also were eligible to receive laser treatment (recorded as concomitant medication during the extension study) at a minimum interval of 90 days, according to the ETDRS guidelines at the investigators' discretion. Decisions on treatment with laser were independent of decisions to inject ranibizumab and vice versa. If in the opinion of the investigator, both ranibizumab and laser treatment were required on the same day, laser was always administered before ranibizumab injection.

Efficacy and Safety Assessments

Efficacy Assessments. The BCVA of the study eye (evaluated through the change vs. baseline of core and extension studies, proportion of patients gaining and losing ≥10 and ≥15 BCVA letters, respectively, and the proportion of patients with BCVA score >78 and <39 ETDRS letters was assessed at every visit as described previously.[11] The VA measurements were taken in a sitting position using the ETDRS-like VA testing charts at a testing distance starting at 4 m. The VA was assessed by certified personnel to ensure standardized BCVA assessments at each visit before applying any potential new dose of ranibizumab.

Anatomic end points included change in CRST (assessed by Stratus Optical Coherence Tomography; Carl Zeiss Meditec Inc., Dublin, CA), proportion of patients with a 3-step change from baseline in the ETDRS severity score, and retinal ischemia (reported as change from baseline in foveal avascular zone, evaluated through the central subfield capillary loss variable) and were assessed as described previously.[11] These end points were assessed by the Central Reading Center.

The patients' subjective assessment of visual functioning was assessed using the National Eye Institute Visual Functioning questionnaire-25 (NEI VFQ-25). The assessed end points included change in NEI VFQ-25 scores (composite, general vision, near activities, and distance activities).

Treatment Exposure. The number and frequency of ranibizumab injections and active laser treatments (recorded as concomitant medication during the extension study) were evaluated during the extension study. Reasons for ranibizumab treatment interruption in the extension study were documented.

Safety Assessments. Safety assessments included monitoring and recording all ocular and nonocular AEs and serious AEs (SAEs). Safety was assessed by standard ophthalmic examinations, IOP measurements, vital signs, and laboratory parameters, as described previously.[11] Laboratory assessments for safety parameters were performed by a certified central laboratory. All ocular/nonocular AEs and SAEs, including information on their relationship to study drug/procedure, were recorded at every visit. Adverse events were summarized by the proportion of patients experiencing any type of AEs and grouped per the standardized Medical Dictionary for Regulatory Activities system organ classes and preferred terms.

The AEs of potential safety concerns (hypersensitivity, hypertension, nonocular hemorrhage, proteinuria, myocardial infarction, venous thromboembolic events, and other arterial thromboembolic events), identified on the basis of prior experience with ranibizumab in clinical trials, were recorded.

Statistical Analysis

All analyses in the extension study were presented by treatment groups as in the core study, namely, ranibizumab, ranibizumab + laser, and laser alone, and are now referred to as prior ranibizumab, prior ranibizumab + laser, and prior laser groups, respectively. No comparison of treatment groups by means of statistical hypothesis testing was intended. Data were summarized for 2 time periods: (1) 24-month analysis (analysis of data from the extension study, i.e., months 12–36) and (2) 36-month analysis (analysis of data from the core and extension studies, i.e., day 1 to month 36).

All analyses were performed on the safety set, consisting of all patients who entered and had at least 1 safety assessment in the extension study. Adverse events were summarized by the number and proportion of patients experiencing AEs by system organ classes and preferred terms. Descriptive statistics (including number of observations, mean, and standard deviation or standard error) were provided separately for each treatment group. A last observation carried forward approach was used for imputation of missing data in the BCVA, CRST, ETDRS severity score, retinal ischemia, and NEI VFQ-25 analysis. All comparisons between day 1 and month 36 and month 12 and month 36 results in this article are made only for the 240 patients who participated in both the core and extension studies.

Results

Patient Disposition and Demographics

Of the 303 patients with DME who completed the core study, 240 provided signed informed consent and were enrolled in the extension study. Although the reasons for nonenrollment into the extension study were not formally documented, the majority of the remaining 63 patients could not be enrolled into the extension study because of administrative reasons, such as late approvals from the institutional review board/independent ethics committee or late contract agreements. All analyses were performed on the safety set, which comprised 83 (prior ranibizumab), 83 (prior ranibizumab + laser), and 74 (prior laser) patients. Of the 240 enrolled patients, 208 (86.7%) completed the extension study (Fig 2, available at www.aaojournal.org). The proportion of patients who completed the study and the month 36 visit was similar

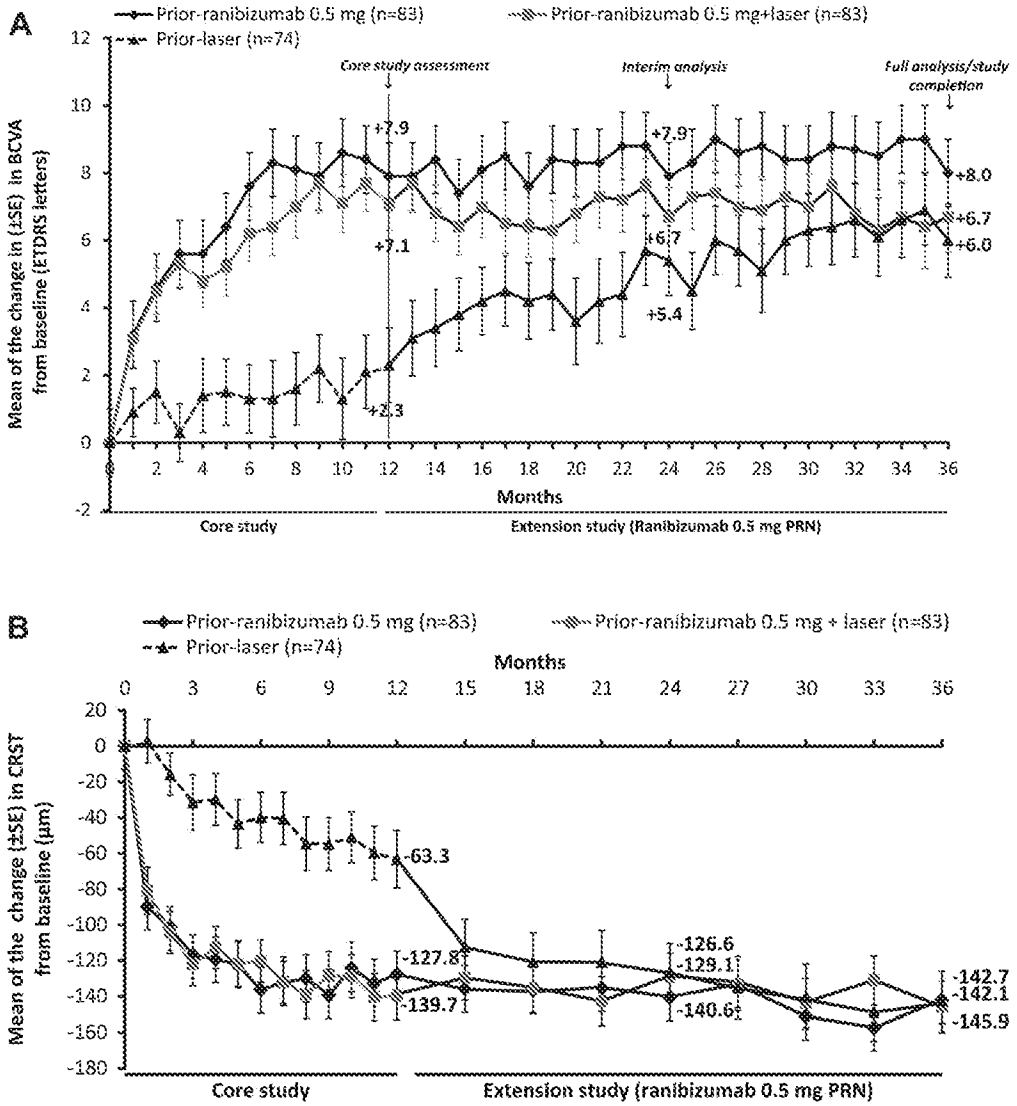


Figure 3. Mean of the change in best-corrected visual acuity (BCVA) letter score from baseline (day 1) to month 36 **(A)** and mean of the change in central retinal subfield thickness (CRST) score from baseline to month 36 **(B)** (safety set [last observation carried forward]). ETDRS = early treatment diabetic retinopathy study; PRN = pro re nata; SE = standard error.

across all the prior treatment groups (prior ranibizumab: 88.0%, prior ranibizumab + laser: 86.7%, and prior laser: 85.1%). Withdrawal of consent (4.6%), death (3.3%), and AEs (2.5%) were the most common reasons for patient discontinuation of the extension study across all the prior treatment groups (Fig 2, available at www.aaojournal.org).

The core baseline demographics and disease characteristics (at day 1) for patients entering the extension study were similar across all the prior treatment groups (Table 1, available at www.aaojournal.org). At the baseline of the extension study (month 12), the disease characteristics of patients treated with laser and those treated with ranibizumab in the core study were comparable except for BCVA, which was slightly lower in patients treated with laser alone in the core study (Table 2, available at www.aaojournal.org).

Efficacy Profile

Best-Corrected Visual Acuity. The mean of the change in BCVA from baseline over 3 years is shown in Figure 3A. In patients treated with ranibizumab in the core study, the mean BCVA gain (letters ± standard error) at month 12 (7.9 ± 0.81 [prior ranibizumab]; 7.1 ± 0.80 [prior ranibizumab + laser]) was in general maintained from month 12 to 36 (prior ranibizumab: 8.0 ± 1.11; prior ranibizumab + laser: 6.7 ± 1.05 at month 36). Of note, prior laser-treated patients, who were eligible to receive ranibizumab treatment in the extension study, showed a progressive improvement of BCVA from 2.3 ± 1.11 letters at month 12 to 6.0 ± 1.09 letters at month 36.

At month 36, 42.2% of patients in the prior ranibizumab group, 28.9% of patients in the prior ranibizumab + laser group, and 17.6% of patients in the prior laser group had a BCVA score >78 letters, whereas only 1 patient (1.2%), 1 patient (1.2%), and 2 patients (2.7%), respectively, had a BCVA of <39 letters at month 36. Over the 3-year study period, a similar proportion of patients gained ≥10 and ≥15 BCVA letters across the 3 groups (Fig 4). However, at month 36, a greater proportion of patients treated with laser alone in the core study lost ≥10 letters (prior ranibizumab: 2.4%; prior ranibizumab + laser: 4.8%; prior laser: 8.1%) and 15 letters (prior

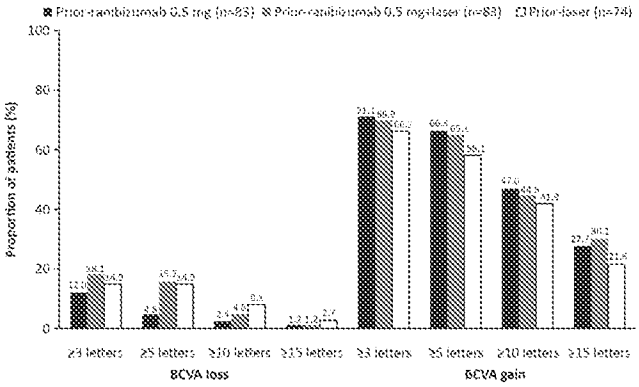


Figure 4. Categorized change in best-corrected visual acuity (BCVA) from baseline (day 1) to month 36 (safety set [last observation carried forward]).

ranibizumab: 1.2%; prior ranibizumab + laser: 1.2%; prior laser: 2.7%) when compared with patients primarily treated with ranibizumab in both the core and extension studies.

Central Retinal Subfield Thickness. In patients treated with ranibizumab in the core and extension studies, the mean CRST reductions observed at the end of the core study (prior ranibizumab: −127.8 μm; prior ranibizumab + laser: −139.7 μm at month 12) were maintained at month 36 (prior ranibizumab: −142.1 μm; prior ranibizumab + laser: −145.9 μm). At month 12, a relatively lower mean reduction in CRST (−63.3 μm) was observed in the prior laser-treated patients compared with patients in the prior ranibizumab group. A progressive reduction of 79.4 μm was observed in the prior laser-treated patients with the allowance of ranibizumab treatment from month 12 to 36 (mean change from baseline to month 36, −142.7 μm; Fig 3B).

Retinal Ischemia. The mean of the changes in the size of the foveal avascular zone from baseline to month 36 were 0.027 mm^2 (median, 0.049 mm^2; prior ranibizumab), 0.051 mm^2 (median, 0.027 mm^2; prior ranibizumab + laser), and −0.399 mm^2 (median, −0.013 mm^2; prior laser).

Early Treatment Diabetic Retinopathy Study Severity Score. At month 36, 14.8% of patients in the prior ranibizumab group, 28.3% of patients in the prior ranibizumab + laser group, and 16.0% of patients in the prior laser group had an improvement in ETDRS severity score (≥3 steps) from baseline, whereas 1.6%, 7.5%, and 4.0% of patients, respectively, had a worsening of ETDRS score (≥3 steps) from baseline to month 36.

Visual Functioning Questionnaire. Over 3 years, patients treated with ranibizumab in both the core and extension studies showed an overall improvement of NEI VFQ-25 scores at month 36 when compared with the core baseline (composite scores: 5.0 [prior ranibizumab], 4.3 [prior ranibizumab + laser]; general vision: 6.0 [prior ranibizumab], 7.1 [prior ranibizumab + laser]; near activities: 12.2 [prior ranibizumab], 7.8 [prior ranibizumab + laser]; distance activities: 2.6 [prior ranibizumab], 4.1 [prior ranibizumab + laser]). In both the prior ranibizumab and prior ranibizumab + laser groups, the initial gains in the NEI VFQ-25 scores observed at month 12 were mostly maintained for the composite (prior ranibizumab: 6.5 [month 12] and 5.0 [month 36]; prior ranibizumab + laser: 4.8 [month 12] and 4.3 [month 36]), general vision (prior ranibizumab: 8.7 [month 12] and 6.0 [month 36]; prior ranibizumab + laser: 8.0 [month 12] and 7.1 [month 36]), distance activity (prior ranibizumab: 6.4 [month 12] and 2.6 [month 36], and near activity (prior ranibizumab: 10.7 [month 12]; 12.2 [month 36]; prior ranibizumab+laser: 9.3 [month 12]; 7.8 [month 36]) prior ranibizumab + laser: 4.5 [month 12] and 4.1 [month 36]) subscale scores until month 36. After allowance of ranibizumab treatment as of month 12, patients in the prior laser group showed a progressive improvement in near activities (month 12: 1.9; month 36: 8.4), general vision (month 12: 1.6; month 36: 8.1), distance activities (month 12: 1.8; month 36: 3.5), and composite scores (month 12: 2.4; month 36: 3.9) from months 12 to 36.

Treatment Exposure

Ranibizumab Injections. Patients who received ranibizumab previously in the core study and continued with individualized ranibizumab treatment in the extension study (prior ranibizumab and prior ranibizumab + laser) received a median of 12.0 (mean: prior ranibizumab [14.2]; prior ranibizumab+laser: [13.5]) ranibizumab injections over 3 years (day 1 to month 35; Table 3 and Table 4, available at www.aaojournal.org). The mean number of ranibizumab injections administered over 2 years of the extension study (months 12−35) was similar across the 3 groups, with a progressive reduction in re-treatment need from the first to the second year and the third year (median, 6.0; mean, 6.8 [prior ranibizumab]; median, 4.0; mean, 6.0 [prior ranibizumab + laser], and median, 4.0; mean, 6.5 [prior laser]). A similar proportion of patients across the 3 groups did not receive any injections over months 12 to 35 (prior ranibizumab: 19.3%; prior ranibizumab + laser: 25.3%; and prior laser: 20.3%; Table 4, available at www.aaojournal.org). Therefore, 59 of the 74 prior laser-treated patients (79.7%) received an average of 8.1 ranibizumab injections from months 12 to 35.

In the 24-month extension study (months 12−35), disease improvement was the most frequent reason for treatment interruption/stop. In the prior laser-treated patients, ranibizumab injections over months 12 to 35 resulted in disease improvement and subsequent treatment interruption in 93.2% of patients (Table 5, available at www.aaojournal.org).

Laser Treatment. The mean number of laser treatments administered to the study eye during the extension study (months 12−36; recorded as concomitant medication) ranged from 0.1 to 0.4 across the prior treatment groups (median, 0.0 for all treatment groups). In the extension study, the majority of patients (75.9%−91.6%) across all groups did not require/receive laser treatment (Table 6, available at www.aaojournal.org).

Safety Profile

Serious Adverse Events. Overall, ocular SAEs (study eye) were reported in 8 patients (3.3%; Table 7, available at www.aaojournal.org) over the 3-year study period (day 1 to month 36); the most frequently observed ocular SAE was cataract (prior ranibizumab + laser: 3 [3.6%], prior laser: 2 [2.7%]). The most frequently occurring ocular SAEs in the extension study (months

Table 3. Mean Number of Ranibizumab Treatments Received over 3 Years (Day 1 to Month 35, Safety Set)

	Mean No. of Ranibizumab Injections		
Treatment Period	*Prior Ranibizumab 0.5 mg (n = 83)*	*Prior Ranibizumab 0.5 mg + Laser (n = 83)*	*Prior Laser (n = 74)*
Day 1 to month 35	14.2	13.5	6.5*
Day 1 to month 11	7.4	7.5	0.0
Months 12−23	3.9	3.5	4.1
Months 24−35	2.9	2.5	2.4

*Includes ranibizumab 0.5 mg injections given over months 12−35 only.

Table 9. Most Frequent Ocular (Study Eye) and Nonocular Adverse Events in the Extension Study (Months 12–36; ≥5% in Any Group, Safety Set)

Preferred Terms	Prior Ranibizumab 0.5 mg (n =83)	Prior Ranibizumab 0.5 mg + Laser (n = 83)	Prior Laser (n = 74)
Ocular AEs (study eye), total	47 (56.6)	47 (56.6)	37 (50.0)
Eye pain	9 (10.8)	6 (7.2)	9 (12.2)
Cataract	7 (8.4)	12 (14.5)	8 (10.8)
Dry eye	3 (3.6)	3 (3.6)	5 (6.8)
Lacrimation increased	2 (2.4)	3 (3.6)	5 (6.8)
Macular fibrosis	1 (1.2)	2 (2.4)	4 (5.4)
Nonocular AEs, total	61 (73.5)	61 (73.5)	53 (71.6)
Nasopharyngitis	12 (14.5)	12 (14.5)	15 (20.3)
Influenza	7 (8.4)	6 (7.2)	7 (9.5)
Hypertension	7 (8.4)	7 (8.4)	5 (6.8)
Back pain	3 (3.6)	2 (2.4)	5 (6.8)
Dizziness	2 (2.4)	0 (0.0)	4 (5.4)
Renal failure	0 (0.0)	2 (2.4)	4 (5.4)

AE = adverse event.
Data are no. (%). Preferred terms are sorted in descending frequency, as reported in ranibizumab 0.5 mg column; a subject with multiple occurrences of an AE under 1 treatment is counted only once in the AE category for that treatment.

12–36) are presented in Table 8 (available at www.aaojournal.org). During the extension study (months 12–36), cataract was observed as an ocular SAE in 1 patient in the prior ranibizumab + laser group. Over the 3-year study period, none of the ocular SAEs of the study eye were suspected by the investigator to be related to the study drug or procedure.

Overall, 88 patients (36.7%) experienced nonocular SAEs (Table 7, available at www.aaojournal.org) over 3 years (prior ranibizumab: 30 [36.1%], prior ranibizumab + laser: 31 [37.3%], and prior laser: 27 [36.5%]). The key nonocular SAEs reported over this 3-year period included coronary artery disease (prior ranibizumab: 3 [3.6%]; prior laser: 1 [1.4%]), angina pectoris (prior ranibizumab: 2 [2.4%]; prior ranibizumab + laser: 1 [1.2%]), cardiac failure (each prior ranibizumab group: 1 [1.2%]; prior laser: 4 [5.4%]), cerebrovascular accident (prior ranibizumab: 2 [2.4%]; prior ranibizumab + laser: 1 [1.2%]; prior laser: 1 [1.4%]), and myocardial infarction (prior ranibizumab + laser: 3 [3.6%]; prior laser: 3 [4.1%]). Nonocular SAEs reported during the extension study (months 12–36) are presented in Table 8 (available at www.aaojournal.org), and those suspected by the investigator to be related to the study drug/procedure over 2 years are indicated.

Of the 240 patients entering the extension, 8 deaths were reported during the 24-month extension study, that is, over months 12 to 36 (2 in the prior ranibizumab group and 3 each in the prior ranibizumab + laser and prior laser groups); none were suspected to be related to the study drug or procedure. Nonocular SAEs reported during the extension study (months 12–36) are presented in Table 8 (available at www.aaojournal.org), and those suspected by the investigator to be related to the study drug/procedure over 2 years are indicated.

Adverse Events. The most frequently observed ocular AEs in the study eye during the extension study (months 12–36) were cataract (27 [11.3%]) and eye pain (24 [10.0%]); the most frequently occurring ocular AEs in the study eye during the extension study (months 12–36; ≥5% in any group) are summarized in Table 9. The most frequent ocular AEs (≥5% in any group; summarized in Table 10, available at www.aaojournal.org) in the study eye across the treatment groups over the 3 years were cataract (39 [16.3%]), eye pain (37 [15.4%]), conjunctival hyperemia (21 [8.8%]), and conjunctival hemorrhage (18 [7.5%]). Of the 240 patients entering the extension study, increased IOP in study eye was observed in 9 patients (3.8%) only across the prior ranibizumab treatment arms over 3 years. The most frequent ocular AEs in the study eye suspected by the investigator to be related to study drug/procedure across all treatment groups over the 3 years (day 1 to month 36) and during the extension study (months 12–36) were eye pain and conjunctival hemorrhage (the latter was observed only in patients who received ranibizumab in the core or extension studies) (Tables 11 and 12, available at www.aaojournal.org). No cases of endophthalmitis were reported in any of the treatment arms over the entire 3-year study period.

Nasopharyngitis (39 [16.3%]), influenza (20 [8.3%]), and hypertension (19 [7.9%]) were the most common nonocular AEs reported in the extension study (months 12–36). The most frequently occurring ocular and nonocular AEs in the extension study were comparable across all groups (Table 9). Nasopharyngitis (56 [23.3%]) and hypertension (32 [13.3%]) were the most common nonocular AEs reported from day 1 to month 36, followed by influenza (28 [11.7%]) and back pain (20 [8.3%]) (Table 10, available at www.aaojournal.org). Nonocular AEs suspected to be related to the study drug/procedure over day 1 to month 36 and months 12 to 36 are summarized in Tables 11 and 12 (available at www.aaojournal.org), respectively.

Adverse Events Leading to Study Drug Discontinuation. Over the 3-year study period, 1 patient each in the prior ranibizumab + laser and prior laser groups experienced ocular AEs in the study eye, leading to study drug discontinuation (Table 13, available at www.aaojournal.org). Nonocular AEs leading to study drug discontinuation over 3 years are summarized in Table 13 (available at www.aaojournal.org).

Adverse Events Related to Potential Safety Concerns. Adverse events related to potential safety concerns over 3 years and in the extension study are summarized in Tables 14 and 15, respectively (available at www.aaojournal.org). No cases of endophthalmitis, retinal tear, or retinal detachment were observed in the extension study.

Discussion

The 3-year results from the RESTORE core and extension studies provide robust data on the long-term safety profile

and the re-treatment need of intravitreal ranibizumab in patients with DME. Patients were treated on the basis of an individualized as-needed regimen similar to the recommendation in the EU label. Therefore, the findings of this study may closely reflect outcomes expected in routine clinical practice with ranibizumab treatment for DME based on the EU label.

At month 12, the RESTORE extension patients initially treated with ranibizumab showed a considerable improvement in BCVA compared with those treated with laser alone in the core phase. During the extension study, patients in the prior ranibizumab groups were able to maintain the initial BCVA gains achieved at month 12 to months 24 and 36 with individualized ranibizumab treatment. Moreover, prior laser-treated patients who could receive individualized ranibizumab treatment at a later stage only (i.e., as of month 12) also achieved BCVA gain from month 12 to months 24 and 36. However, at month 24, the BCVA gain from core baseline observed in the prior laser group was around 75% of that achieved in the prior ranibizumab groups. At month 36, the patients in the prior laser group demonstrated a BCVA gain similar to that observed in the prior ranibizumab groups, but a gradual BCVA gain was observed in the prior laser group over a period of 3 years when compared with the rapid initial gain observed in the prior ranibizumab-treated patients. We hypothesize that prolonged edematous stress due to deferred ranibizumab treatment and subsequent damage to neurosensory layers may have led to the delayed VA gain observed in the prior laser-treated patients. However, this study was not designed to test this hypothesis; further investigations are required to evaluate the retinal damage associated with deferred ranibizumab treatment and consequently to determine the appropriate timing for the initiation of ranibizumab treatment.

The proportion of patients gaining $\geq$10 letters or $\geq$15 letters was somewhat similar across the 3 treatment groups at month 36. However, a greater proportion of patients in the prior laser group lost $\geq$10 letters and $\geq$15 letters than those in the prior ranibizumab and prior ranibizumab + laser groups, underscoring the value of early ranibizumab therapy in reducing the risk of significant BCVA loss.

In patients treated with ranibizumab in the core and extension studies, mean CRST decrease at month 12 was maintained from month 12 to month 36. However, in patients treated with laser alone in the core study, mean CRST observed at month 12 further decreased through month 36 with the allowance of ranibizumab in the extension study. This finding demonstrates the anatomic effectiveness of ranibizumab even in patients with long-standing DME. It is reassuring that ranibizumab treatment over 3 years in the prior ranibizumab groups or over 2 years in the prior laser group was not associated with a considerable progression in the foveal avascular zone. Furthermore, a greater proportion of patients showed an improvement rather than worsening of ETDRS severity scores with ranibizumab treatment over the 3-year study period.

In addition to the improvements in BCVA and CRST from baseline to month 36, there was an overall improvement in patient-reported visual functioning, as measured by the NEI VFQ-25 subscale scores (composite, general vision, near activities, and distance activities) in patients who received continuous ranibizumab treatment from the core study. A substantial portion of the initial gain in the NEI VFQ-25 scores was maintained in the prior ranibizumab groups even with a low mean number of injections during the extension study. Patients in the prior laser-treated group showed an improvement in the NEI VFQ-25 subscale scores from month 12 to months 24 to 36 after receiving ranibizumab treatment in the extension study; however, for patients in the prior laser group, a period of approximately 3 years was required to achieve visual functioning benefits similar to those in the prior ranibizumab groups. Because DME affects the working-age population,[1] any delay in VA gains may significantly affect their ability to perform day-to-day activities. Therefore, it is important to initiate prompt ranibizumab treatment to provide VA benefits at the earliest opportunity.

One of the most relevant and beneficial findings of this long-term analysis is certainly the change in re-treatment need over time. The individualized dosing regimen based on VA stability and disease progression criteria was able to maintain VA and provide optimal visual function benefits in prior ranibizumab-treated patients with decreasing frequency of injections over time. The mean number of injections received by the ranibizumab-treated patients from day 1 to month 5 was 4.9 (median, 5.0) injections, including the 3 mandatory loading injections. Patients treated with ranibizumab from the core phase received an average of 13.9 injections (median, 12.0 injections) from day 1 to month 35, with an average of 3.7 injections during the first year of the extension study, which further decreased to 2.7 injections in the final year of the extension. Approximately 19% to 25% of patients across the treatment arms did not require any ranibizumab injections during the extension study. Therefore, patients treated with ranibizumab during the entire study were, on average, able to maintain the BCVA gained up to month 12 with fewer than 3 injections during the final year of the extension with the protocol-specified re-treatment criteria. Almost every patient (93.2%–100%) interrupted treatment at least once from months 12 to 35 because of disease improvement.

The RESTORE extension results mirror those of the DRCR.net study[9] in which, over a period of 3 years, VA was maintained with a diminishing number of injections. However, in the DRCR.net study there were only ranibizumab + prompt laser or ranibizumab + deferred laser arms, excluding the possibility of evaluating whether ranibizumab monotherapy could be as effective when compared with ranibizumab combined with prompt or deferred laser. Also, in contrast to the DRCR.net study, the current study assessed the effects of ranibizumab monotherapy over 3 years, although concomitant laser treatment was allowed in the extension study. The re-treatment criteria used in the current study are consistent with the ranibizumab EU label and are simple to apply in the context of clinical practice.[9]

The long-term RESTORE extension study provides valuable information regarding the individualized dosing regimen of ranibizumab during extended treatment in DME. The progressive reduction in re-treatment needs is the most

positive conclusion and provides the opportunity to further optimize the management of DME. However, it was beyond the scope of this study to determine whether an alternate treatment strategy such as "treat and extend" or PRN treatment with less frequent than monthly monitoring could result in a similar visual outcome compared with PRN dosing, while potentially reducing the need for monthly monitoring. Such an outcome is likely, given the ability to extend follow-up intervals as found in the DRCR.net protocol.[9] Unlike the individualized dosing regimen used in the current study, a treat and extend regimen provides treatment at any follow-up visit but increases the interval to the next visit if vision is stable. The RETAIN study (registered as NCT01171976 at http://clinicaltrials.gov/; accessed June 25, 2013) is expected to provide valuable information regarding the efficacy and safety of ranibizumab using an alternate treat and extend dosing regimen.

Establishing the long-term safety profile of retinal vascular disease treatments is extremely important because the retinal microvasculature is closely interlinked with the cerebral microvasculature and abnormalities of the retinal microvasculature are important predictors of cardiovascular risks and mortality.[13,14] Thus, any insult to the retinal microvasculature may have an impact on the brain and cardiovascular system. In addition, patients with DME are also prone to systemic complications associated with diabetes,[2] which further mandates the long-term safety monitoring of any treatments administered to these patients.

The results of this 3-year long-term study demonstrated that ranibizumab treatment was generally well tolerated, with no new ocular or systemic safety findings, consistent with the safety observations in the RESTORE core and interim studies.[11,12] In the current study, ocular SAEs were reported in 2.4% to 4.1% of the patients across the treatment arms over 3 years, and the majority of the reported SAEs were not suspected to be related to the study drug/procedure.

During the 3-year study period, a total of 2779 ranibizumab injections were administered, with no reports of endophthalmitis, suggesting that there was adequate adherence to the aseptic injection procedure. Throughout the study period, the most frequently reported ocular AEs were cataract (16.3%) and eye pain (15.4%), and the most frequently reported nonocular AEs were nasopharyngitis (23.3%) and hypertension (13.3%), which were reported in similar frequencies across the 3 prior treatment groups. Among the 240 patients entering the extension study, 8 deaths were reported, none of which were suspected to be related to the study drug/treatment procedure. The safety profile of ranibizumab in this 3-year study is consistent with the safety profile of ranibizumab observed in other DME trials and in trials involving patients with age-related macular degeneration and retinal vein occlusion.[6–9,11,12,15–19]

In terms of study limitations, patients with stroke and transient ischemic attack were excluded from this study in contrast to the real-life setting where there is a possibility that a more diverse patient population with multiple comorbid conditions would receive ranibizumab therapy. Thus, the safety results of this study should be interpreted relative to this exclusion. In addition, this extension study enrolled 240 patients and was not powered to assess the occurrence rate of infrequent but important SAEs, including systemic events (e.g., stroke). Long-term studies such as LUMINOUS (registered as NCT01318941 at http://clinicaltrials.gov/; accessed June 25, 2013) conducted in a broad patient population will help to further describe the long-term safety profile, effectiveness, and treatment patterns of ranibizumab in a real-life setting.

In conclusion, the 3-year results of the RESTORE extension study confirmed the favorable efficacy and safety profiles of ranibizumab in the long-term treatment of visual impairment due to DME. Ranibizumab treatment was generally well tolerated, and there were no new ocular or systemic AEs. The safety profile of ranibizumab observed in this study is consistent with the well-established safety profile of ranibizumab. This study also demonstrated that individualized treatment was able to consistently maintain VA in the ranibizumab-treated patients. Of note, the number of injections required during the extended follow-up declined progressively, enabling optimized strategies for long-term management of DME with intravitreal ranibizumab. Across the 3 treatment arms, 19% to 25% of patients did not require any ranibizumab injections during the extension study. Therapeutic benefit of ranibizumab was also observed in the prior laser-treated patients, who could receive ranibizumab only during the extension study. Although patients in the prior laser group were finally able to achieve approximately 75% of the benefit seen in the ranibizumab monotherapy group, after receiving ranibizumab in the extension study, this gain was gradual and occurred over the 2-year period of the extension. Thus, early initiation of ranibizumab therapy may provide prompt and substantial VA gains allowing patients from the working-age population, often challenged by multiple systemic comorbidities, to ease disease management and improve quality of life despite severe and chronic disease.

Acknowledgments. The authors thank Srividdya Agoram and Ruchika Srinivasan (Medical Communications, Novartis Healthcare Pvt. Ltd.) for providing medical writing support. This encompassed supporting the preparation and revision of drafts, including editorial support, all under the direction of the authors.

References

1. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes Care 2003;26:2653–64.
2. Fu AD, Yang SS, McDonald HR. The clinical management of diabetic retinopathy. Adv Stud Ophthalmol. October 2004:18–29. Available at: http://www.jhasio.com/template.cfm?TEMPLATE=include_programinfo.cfm&ID=4&ZoneID=10&TYPE=text. Accessed November 24, 2013.
3. Dowler JG. Laser management of diabetic retinopathy. J R Soc Med 2003;96:277–9.
4. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26:859–70.
5. Lucentis. Summary of product characteristics. Section 4.1 Therapeutic indications. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/

human/000715/WC500043546.pdf. Accessed November 24, 2013.
6. Nguyen QD, Brown DM, Marcus DM, et al; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789–801.
7. Diabetic Retinopathy Clinical Research Network, Writing Committee, Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118:609–14.
8. Nguyen QD, Shah SM, Khwaja AA, et al; READ-2 Study Group. Two-year outcomes of the Ranibizumab for Edema of the Macula in Diabetes (READ-2) study. Ophthalmology 2010;117:2146–51.
9. Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 2012;119:2312–8.
10. Do DV, Nguyen QD, Khwaja AA, et al; READ-2 Study Group. Ranibizumab for Edema of the Macula in Diabetes study: 3-year outcomes and the need for prolonged frequent treatment. JAMA Ophthalmol 2013;131:139–45.
11. Mitchell P, Bandello F, Schmidt-Erfurth U, et al; RESTORE Study Group. The RESTORE Study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615–25.
12. Lang GE, Berta A, Eldem BM, et al; RESTORE Extension Study Group. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the RESTORE Extension Study. Ophthalmology 2013;120:2004–12.
13. Witt N, Wong TY, Hughes AD, et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. Hypertension 2006;47:975–81.
14. Patton N, Aslam T, MacGillivray T, et al. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat 2005;206:319–48.
15. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 2010;33:2399–405.
16. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
17. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
18. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology 2011;118:1594–602.
19. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology 2011;118:2041–9.

Footnotes and Financial Disclosures

Originally received: July 23, 2013.
Final revision: November 19, 2013.
Accepted: November 26, 2013.
Available online: February 3, 2014. Manuscript no. 2013-1212.

[1] Department of Ophthalmology, Medical University Vienna, Vienna, Austria.

[2] Division of Medical Retina and Laser Surgery, Department of Ophthalmology, University Eye Hospital Ulm, Ulm, Germany.

[3] Department of Ophthalmology, University of Bonn, Bonn, Germany.

[4] Medical Retina Unit and Ocular Angiogenesis Group, Department of Ophthalmology, Academic Medical Center, Amsterdam, The Netherlands.

[5] Netherlands Institute for Neuroscience (NIN), Royal Academy of Sciences (KNAW), Amsterdam, The Netherlands.

[6] Department of Ophthalmology, University of Udine, Udine, Italy.

[7] Istituto Europeo di Microchirurgia Oculare (IEMO), Udine, Italy.

[8] Assistance Publique des Hopitaux de Paris, Université Paris Diderot, Ophthalmology Department, Hopital Lariboisiere, Paris, France.

[9] Novartis Pharma AG, Basel, Switzerland.

[10] Beijing Novartis Pharmaceuticals Co., Ltd., Shanghai, China.

[11] Centre for Vision Research (Westmead Millennium Institute), University of Sydney, Sydney, Australia.

Data from this study were presented at: The Association for Research in Vision and Ophthalmology, May 6–10, 2012, Ft. Lauderdale, Florida; EASDec, May 25–27, 2012, Dublin, Ireland; Club Jules Gonin, June 20-23, 2012, Reykjavik, Iceland; EURETINA, September 6–9, 2012, Milan, Italy; European Association for the Study of Diabetes, October 1–5, 2012, Berlin, Germany; American Academy of Ophthalmology, November 10–13, 2012, Chicago, Illinois; and Asia Pacific Academy of Ophthalmology, January 17–20, 2013, Hyderabad, India.

Financial Disclosure(s):
The author(s) have made the following disclosure(s):

U.S.-E.: Bayer Health Care, Alcon, Novartis, Allergan, Boehringer (consultant fee).

G.E.L.: University Eye Hospital, Ulm (grant, consulting fee); Novartis (research grant, consultant, fees for lecture, clinical studies); Alcon (consultant); Allergan (clinical studies).

F.G.H.: Novartis (grant, support for travel to meetings for the study or other purposes, consulting fee); Heidelberg Engineering, Novartis, Pfizer, Acucela, Genentech, Alcon, Allergan (consultant); Novartis, GlaxoSmithKline, Alcon, Optos, Heidelberg Engineering, Carl Zeiss Meditec, Allergan (Grants); Alcon, Pfizer, Novartis, Heidelberg Engineering, Bayer Healthcare (lecture fees).

R.O.S.: Novartis, Boehringer Ingelheim (board membership); Novartis (grants, lecture fees, consulting fees).

P.L.: Alimera, Allergan, Alcon, Bayer, Novartis, Roche (personnel fees); Novartis (grants).

P.M.: Novartis, Allergan (board membership); Novartis, Allergan, Sanofi, Bayer (consultant).

O.G.: full-time employee of Novartis Pharma AG.

A.S.B.: full-time employee of Novartis Pharma AG.
H.S.: full-time employee of Beijing Novartis Pharmaceuticals Co.

A.O.: full-time employee of Novartis Pharma AG.
P.M.: Novartis, Bayer, Abbott (consultant, lecture fee).

Sponsored by Novartis Pharma AG, Switzerland, and the study is registered with http://clinicaltrials.gov/; accessed June 25, 2013 (NCT00906464).

Correspondence:
Ursula Schmidt-Erfurth, MD, Department of Ophthalmology, Medical University Vienna, Waehringer Guertel, 18-23 Vienna, Austria. E-mail: ursula.schmidt-erfurth@meduniwien.ac.at.

Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration

RICHARD SPAIDE

AGE-RELATED MACULAR DEGENERATION (AMD) IS increasing in incidence and prevalence among the world's population. Inhibition of the vascular component of AMD has been attempted with a variety of approaches, but the development of the pan-vascular endothelial growth factor (VEGF)-A blocker, ranibizumab (Lucentis, Genentech, South San Francisco, California, USA), for the treatment of choroidal neovascularization (CNV) has been a triumph of modern medicine.[1] Ranibizumab is an antibody fragment that binds all active isoforms of VEGF-A, rendering them inactive. It was developed through an exhaustive process that required modifying a murine monoclonal antibody to derive an antibody fragment, and affinity maturing the fragment to restore and even improve VEGF binding. Patients with neovascular AMD treated in phase 3 trials using this medication experienced an improvement in visual acuity. In the MARINA trial, which examined minimally classic or occult with no classic disease, patients receiving 0.5 mg of intravitreal ranibizumab on a fixed monthly schedule had a mean improvement of 7.2 letters, while sham-treated controls lost 10.4 letters over the course of the first year.[2] In the ANCHOR trial, patients receiving 0.5 mg of intravitreal ranibizumab on a fixed monthly schedule had a mean improvement of 11.3 letters, while controls treated with photodynamic therapy that used verteporfin had a mean loss of 9.5 letters over the first year.[3]

Along with the triumph of ranibizumab comes the bill. The drug charge per injection costs patients, or their insurance company, $2,000. The costs estimate increases when the charges for the injection procedure, the ophthalmic examination, and associated tests are added. Economists would add in the costs incurred by the family members taking off work to accompany the patient and lost opportunity costs. The total cost over a year for a single patient is stunning; the cost projections for the United States are staggering. Although economists can convert burdens into the equivalent economic ones, patients and doctors alike often pigeonhole costs. Returning every month for injection and follow-up within two to seven days after the injection, as recommended in the product insert, is a cost, but also is an emotional and psychological burden for the patient, family, and even the doctor. In medicine, risk of treatment is usually associated with the intensity of treatment. Mandated monthly treatment may incur increased risks, particularly if the patient really doesn't really "need" the treatment each month.

In this issue appears an important article by Anne Fung and associates at Bascom Palmer Eye Institute.[4] This study, known as the Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intraocular Ranibizumab (Lucentis), or PrONTO, study, led by Phil Rosenfeld, examined a strategy of giving patients ranibizumab on a schedule dictated by a carefully considered list of criteria. At baseline and each visit thereafter, patients had their visual acuity measurements performed with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 2 m when a refraction protocol was used. Patients then were given three injections of ranibizumab at monthly intervals. Five criteria were used to determine whether a patient needed an additional injection at each monthly follow-up examination. Patients were treated again if they had a visual acuity loss of at least 5 letters on the ETDRS chart with optical coherence tomography (OCT) evidence of fluid in the macula, an increase in OCT central retinal thickness of at least 100 μm, new macular hemorrhage, new area of classic CNV seen by fluorescein angiography, or evidence of persistent fluid on OCT at least one month after the previous injection. After one year of follow-up, the patients had a mean visual acuity improvement of 9.3 letters. With the usual caveats about comparing studies, the visual acuity results were similar to those seen in ANCHOR and MARINA. However, patients in the PrONTO study required only 5.6 injections over the first year. The reduced drug costs per patient amount to about half the mean per capita yearly income for older people in the United States.[5] Multiply this dollar amount by the number of patients with CNV that results from AMD and the potential savings are enormous.

If patients can meet the entry criteria of the study and are treated according to the methods used in the study, they would have a reasonable expectation of having similar results. The confidence of this expectation is influenced by a number of factors, including the number of patients in the study. The ANCHOR and MARINA studies both had large numbers of patients, whereas the PrONTO study had 40 patients and no controls. In actuality, PrONTO would

See accompanying Article on page 566.
Accepted for publication Feb 9, 2007.
From the Vitreous, Retina, Macula Consultants of New York, New York, New York.

Inquiries to Richard Spaide, Vitreous, Retina, Macula Consultants of New York, 460 Park Ave, 5th Floor, New York, NY 10022; e-mail: rickspaide@yahoo.com

0002-9394/07/$32.00
doi:10.1016/j.ajo.2007.02.024

be difficult to implement for many practices. An ETDRS visual acuity measurement with protocol refraction is a requirement for a rigorous trial and is a time-consuming test administered by a certified visual acuity examiner. This test is not practical for many busy practices. Dropping the need for ETDRS visual acuity measurement as part of the criteria would make the study easier to implement, but at the cost of widened confidence intervals for the expected outcomes.

The reduction in intraocular injections was not associated with marked reduction in visits by the patient to the ophthalmologist's office. Patients still required monthly examinations with monthly OCTs and quarterly fluorescein angiograms to look for classic CNV. An alternative approach would be to look for a method to decrease both the injections and visits in general. In the PIER trial, patients were provided three injections at monthly intervals and then quarterly injections, except the patients were given a final injection at month 11. Even though the patients should have had a fairly good 12-month visual acuity because they had a mandated injection at 11 months, the mean visual acuity dropped by 0.2 letters in the 0.5-mg group. So giving the patients a reduced number of injections—a therapy not based on objective factors of need—appeared to result in a less favorable outcome.[6] In our office, we treat some patients with a technique we call "inject and extend." Patients are provided three monthly injections and then told to return in six weeks. They undergo an ophthalmic examination, including biomicroscopy and OCT. If the patients have no new hemorrhage or signs of exudation such as edema or subretinal fluid they are injected and instructed to return in eight weeks. If they have edema or other signs of exudation, they are given an injection and told to return in four weeks. Patients returning at eight weeks are given the same examination. If there are no signs of disease activity, they are given an injection and told to return in 10 weeks. If they have exudation, they are given an injection and told to return in six weeks. Patients with this strategy would go only a few weeks, at most, of having any sign of exudation. The optimal examination and treatment interval may be quickly established.

It is obvious that monthly treatment is an expensive and burdensome ordeal. The good news is that it works. The PrONTO approach obviates the need for six injections, but still has the cost of monthly examinations. The good news about PrONTO is that it suggests that patients can be treated according to need and have a good outcome. We need to determine and consider what the patient's needs are in aggregate. How can we best address the patient needs, both for good visual outcome and decreased burden to the patient and the patient's family? What are the best criteria to use for retreatment? Is an inject and extend strategy better because it reduces patient visits? These are interesting questions that need to be answered. They could not have been asked without the groundbreaking work of the Bascom Palmer group with the PrONTO study, which to their credit was partly funded by Genentech, the maker of ranibizumab.

THE AUTHOR RECEIVED CONSULTING FEES AND RESEARCH SUPPORT FROM GENETECH (SOUTH SAN FRANCISCO, CALIFORNIA, USA) and Novaritis (East Hanover, New Jersey, USA). The author was involved in design and conduct of study; data collection; analysis and data interpretation; and preparation and manuscript writing and approval.

REFERENCES

1. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006; 26:859–870.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444.
4. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An OCT guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmology 2007;143:566–583.
5. Wu KB. Sources of income for older persons 2003. Available at: http://assets.aarp.org/rgcenter/econ/dd125_income.pdf. Accessed Date: February 9, 2007.
6. Genentech press release concerning the PIER study. Available at: http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9747. Accessed Date: February 9, 2007.

Regeneron Focuses on Age-Related Macular Degeneration

Wendy Wolfson
DOI 10.1016/j.chembiol.2008.04.002

For some people, the onslaught of time brings another loss: the erosion of central vision, making it impossible to drive or read a book or see the contours of a loved one's face. No one knows what precipitates age-related macular degeneration (AMD), but it is the leading cause of vision loss among the elderly in western countries. Aside from getting old, the major risk factors for AMD include smoking and having a genetic predisposition.

Approximately 15–20 million Americans suffer from AMD, with about 200,000 new cases diagnosed each year and 3–4 million legally blind as a result. No cure exists; current therapies can slow disease progression in a limited number of cases, but do not address the underlying cause.

It was remarkable, the closest thing to penicillin we had ever seen.

The macula is a small patch in the middle of the retina that contains a high concentration of photoreceptor cells which transmit visual signals to the brain and governs central vision. Macular degeneration takes two forms: the early atrophic, or "dry," and the more advanced exudative, or "wet," version. Most people develop the early or intermediate dry form of macular degeneration in which tiny deposits of protein and other cellular debris called drusen accumulate on the macula.

Some patients with dry AMD are helped by doses of vitamins and antioxidants. The Age-Related Eye Disease Study (AREDS) conducted by the National Eye Institute (NEI) showed that antioxidant supplements retarded progression of dry AMD in about one-quarter of cases. NEI is currently recruiting 4000 volunteers for a new study to see the effect of antioxidants (lutein and zeaxanthin) and/or the long-chain omega-3 fatty acids DHA and EPA.

In 10%–15% of patients, AMD abruptly morphs into the more virulent wet type, in which abnormal blood vessels grow uncontrollably beneath the retina, damage the macula, and leak blood and fluid. This process, called choroidal neovascularization (CNV), irreversibly damages the photoreceptor cells.

The first FDA-approved treatment for wet AMD was Visudyne (verteporfin) Photodynamic Therapy (PDT) from QLT and Novartis. Visudyne, a light-activated drug, is injected intravenously to destroy targeted blood vessels. Aside from surgery, other approaches under development include implants to deliver medication.

Sibling Rivalry

In the mid and late 1990s, it became increasingly apparent that vascular endothelial growth factor (VEGF) was a driver for CNV. VEGF antagonists such as Macugen (Pegaptanib), an injectable ribonucleic aptamer, was developed by Pfizer/Eyetech. Macugen was the first VEGF antagonist to get approved, in 2004, but the current gold standard for treating wet AMD is Genentech's Lucentis (ranibizumab), a humanized antibody fragment that binds to different isoforms of VEGF. Approved by the FDA in June 2006, Lucentis is administered by injection into the eye.

Lucentis is descended from the same monoclonal antibody as Avastin (bevacizumab), another Genentech anti-angiogenic approved by the FDA in 2004 for colorectal cancer. Meanwhile, waiting for Lucentis approval, various groups were experimenting with Avastin for wet AMD. Dr. Philip Rosenfeld at the Bascom Palmer Eye Institute reported the results at the American Society of Retinal Specialists in 2005. Rosenfeld wrote in a later paper "The option of using Avastin for $17–$50 a dose is clearly more attractive than PDT at $1500 a treatment or Lucentis at $2000 a dose. Eventually, for us to know which treatment is better, a head-to-head clinical trial is necessary" (Rosenfeld, 2006).

"Six months later, hundreds of thousands of eyes in the US used Avastin." recalled Dr. Daniel Martin, professor of ophthalmology at Emory University Medical School and chair of the current NIH phase III clinical trials comparing Lucentis and Avastin. "It was remarkable, the closest thing to penicillin we had ever seen."

Regeneron Hopes for a Bit of Regeneration

A third player is now entering the Lucentis/Avastin scrimmage. Tarrytown, NY, based Regeneron (http://www.regn.com), a public company, has a compound for wet AMD, VEGF Trap-Eye, in phase III clinical trials. Regeneron's compound is designed to bind VEGF and the related Placental Growth Factor (PLGF). The study is expected to enroll approximately 1,200 patients in North America and will compare VEGF Trap-Eye to Lucentis. In 2006, Bayer Healthcare, LLC, struck a collaboration for VEGF Trap-Eye of $75 million up front and $245 million in milestone payments.

Regeneron's VEGF Trap-Eye approach involves attaching the binding portions of two different receptors to the Fc fragment of an antibody. This constructed molecule blocks signaling proteins from binding to receptors—impeding the formation of leaky blood vessels. According to Neil Stahl, Ph.D., senior vice president, research and development sciences, the VEGF Trap-Eye molecule is smaller than Avastin by ~50% but has ~2000-fold tighter binding than Avastin and 200 times that of Lucentis, affinities arrived at in the test tube but which need confirmation by this clinical trial. "In the closed compartment of the eye, you will get better blockage at lower drug levels." Stahl said. Regeneron is maximizing the half-life of the compound, an important consideration for patients who have to endure injections into their eyes. "A major goal of therapy is

to dry out the eye," Stahl said. "We are also looking at reversing the size of the lesions."

Banking on Eyes

Gregory Hageman, professor of ophthalmology at the University of Iowa, became interested in AMD in the late 1980s. "The real issue is that there were no animal models." Hageman said. "We decided to use human donor eyes to determine what these drusen were comprised of." Hageman accumulated 4000 pairs of eyes, 1000 pairs from AMD patients. He found the drusen contained proteins associated with the complement cascade, a biochemical cascade which helps clear pathogens from an organism, and hypothesized that AMD was caused by inflammation. In 2005, Hageman and several other groups found that AMD was associated with variants of the complement factor B and complement factor H genes. According to Hageman, these genetic variants account for up to 3/4 of cases of early AMD by producing defective proteins that cause immune system malfunction.

Hageman is cofounder and chief scientific officer of Optherion (http://www.optherion.com), which focuses on the earlier dry stage of AMD. Optherion is located in New Haven, CT, and at the University of Iowa. Instead of developing a systemic inflammation inhibitor, Optherion's approach will be to develop an augmented protein protective against AMD.

Orchestrated by biotech investor David Scheer, Optherion received $37 million in financing last year from a consortium of companies and venture capitalists. Optherion licensed its intellectual property from the University of Iowa Research Foundation, Yale, and the University of Pittsburgh on chromosome 10.

No direct inflammatory trigger for AMD has been found yet, although different groups are proposing infections with organisms like chlamydia. "The thing about inflammation is that we don't know whether it is the cause or the result of the disease process." says Margaret DeAngelis, Ph.D., assistant professor of ophthalmology at Harvard Medical School and Massachusetts Eye and Ear Infirmary. Her group and others are studying the entire complement pathway to identify its precise role in AMD.

DeAngelis pointed out that while genes like complement factor H have variants associated with risk "...there are a lot of people in the population walking around with these variants that don't have the disease." And what causes dry AMD to turn to wet AMD? "We'd love to know," said DeAngelis. Part of the problem, according to DeAngelis, is lack of a good animal model, as the mouse has a retina but not a macula. "The identification of CFH was a phenomenal stepping stone in beginning to develop a molecular biochemical profile for AMD risk" said DeAngelis. "From a chemical or biochemical standpoint it will be important to correlate our genetic findings at the protein level so that appropriate agonists and antagonists can be developed for treating this devastating form of blindness."

Better Than a Poke in the Eye If They Can Get It to Work

San Diego-based TargeGen (http://www.targegen.com) hopes to dispense with the eye injections entirely and administer its wet macular degeneration, diabetic macular edema, and diabetic retinopathy treatment as eyedrops. The company's compound TG100801 is a benzotriazine inhibitor that targets the VEGF pathway. Specifically, their compound inhibits VEGFFr2 and members of the SRC kinase family. TargeGen has $36 million in D-round financing.

TG100801 was developed as a prodrug, an ester that is hydrolyzed by esterases to have active effects in the back of the eye. According to Richard Soll, Ph.D., vice president of research and development and chief scientific officer at TargeGen, the challenge was designing a drug for twice daily dosing that could be rapidly cleared from systemic circulation.

But TargeGen's Phase II clinical trials to look at the reduction of edema or leaks in the eye were halted when brown-colored microparticles of the compound appeared just below the cornea. The company is weighing its options: either to continue testing it at a 30× lower dose in an animal model, consider administering it through a device, or switch to another compound in the preclinical cupboard, TG100948, from a different chemical family. "We will make a decision that will probably be made in context of a partner to develop or not," said Soll.

In another go-round, New Jersey-based Ophthotech (http://www.ophthotech.com) was inaugurated in 2007 with $36 million by former Eyetech execs to develop therapies for both dry and wet AMD. The company came with a dowry of three compounds: the first, E10030, an anti-PDGF aptamer, is entering a Phase I trial of up to 36 patients. E10030 is being tested in combination therapy with a VEGF-A inhibitor to see if it can roll back the angiogenesis of wet AMD. Additional compounds include ARC1905, a complement (anti-C5) inhibitor, and volociximab, an anti-angiogenesis monoclonal antibody-targeting $\alpha5\beta1$ integrin. ARC1905 inhibits C5, a trigger of inflammation, which is a part of the complement cascade.

Companies like TargeGen, Optherion, and Ophthotech are harbingers of new strategies such as easier delivery and combining drugs to knock off different parts of the problem. However, "It is all extremely early," Martin said. "I think the anti-VEGF therapies are likely to dominate for a while."

REFERENCE

Rosenfeld, P.J. (2006). Intravitreal avastin: The low cost alternative to lucentis? Am. J. Ophthalmol. *142*, 141–143.

Wendy Wolfson (wendywolfson@nasw.org) is a Bay Area science and technology writer.

NEURO-ONCOLOGY

EDITORIAL

Moving Toward the Next Steps in Angiogenesis Therapy?

The clinical approach of using antibodies that sequester molecules in the bloodstream is an elegant solution to the drug-uptake problem in neuro-oncology. Our recent editorial, "Bevacizumab—News from the Fast Lane?"[1] highlighted the progress and some of the concerns regarding antiangiogenesis therapy for brain tumors; there, we commented on some encouraging results from clinical trials using the humanized antivascular endothelial growth factor (VEGF) antibody bevacizumab that indicated increased patient response rates. Preclinical and clinical data support the benefits of antiangiogenic therapies for cancer; however, the observed benefit is no more than temporary, suggesting the emergence of a resistant phenotype.

A new anti-VEGF agent, VEGF Trap/aflibercept, has been developed by incorporating domains of both VEGFR-1 and VEGFR-2 fused to the constant region of human IgG1, which acts as a soluble decoy receptor for VEGF. In the current issue of *Neuro-Oncology* (see page 940), Gomez-Manzano and colleagues have assessed the role of this new anti-VEGF antibody in a well-established intracranial glioma animal model.[2] Using different treatment schedules and initiating treatment at different times following glioma cell implantation, they conclude that VEGF Trap treatment was efficacious in both initial and advanced phases of tumor development. This antitumor effect was enhanced in animals treated with more prolonged regimens. However, long-term treatment with VEGF Trap resulted in a modified pattern of tumor growth, characterized by the presence of satellitosis consisting of aggregations of glioma cells in the perivascular regions, suggesting acquisition of an invasive phenotype in response to anti-VEGF therapy. Those results seem to coincide with preliminary data from MRI studies of glioblastoma patients treated with bevacizumab, showing the development of multifocal recurrence and strongly indicating the presence of an infiltrative/invasive pattern.[3,4] In this regard, Bergers and Hanahan recently proposed several hypothetical mechanisms that might underlie the evasive resistance to antiangiogenic therapy.[5] These models include an increased capability of the tumor cells to develop an invasive phenotype without promoting angiogenesis. In fact, there is strong evidence that malignant glioma cells adapt to pathological conditions (such as necrosis) or to therapies that challenge angiogenesis, by migrating more aggressively into normal tissue. Collectively, these observations indicate that the clinical success of antiangiogenic therapy, including VEGF Trap, might depend on the establishment of combined therapies aiming to induce tumor regression by inhibiting angiogenesis and to prevent multifocal recurrence by inhibiting tumor infiltration.

Preclinical and clinical data have established the effectiveness of antiangiogenic therapies for human malignant gliomas. However, more studies need to be undertaken, with a special focus on identification of the mechanisms of the resistant phenotype and, ultimately, the testing of combined therapies. The establishment of animal models suitable for these goals and the search for reliable biomarkers of response and resistance to therapy are urgent priorities in the drive to advance the promising field of antiangiogenic therapy. Timely results from a multicenter phase II clinical trial of VEGF Trap in patients with recurrent gliomas will soon be available, and therefore, critical information on these evasive resistant phenotypes and progression patterns might soon be available.[6]

W. K. Alfred Yung, Editor in Chief

Neuro-Oncology 10, 939, 2008 (Posted to Neuro-Oncology [serial online], November 3, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-091)

References

1. Weller M. and Yung W.K.A. Bevacizumab—News from the Fast Lane? *Neuro-Oncology* 2008;10:647.
2. Gomez-Manzano C, Holash J, Fueyo J, et al. VEGF Trap induces antiglioma effect at different stages of disease. *Neuro-Oncology*, 2008; 10:940.
3. Narayana A, Kelly P, Golfinos J, et al. Antiangiogenic therapy using bevacizumab in recurrent high-grade glioma: impact on local control and patient survival. *J Neurosurg. [serial online]* October 3, 2008. Available at http://thejns.org/doi/pdf/10.3171/2008.4.17492.
4. Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology*. 2008;70:779-787.
5. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer*. 2008;8:592--603.
6. de Groot JF, Wen PY, Lamborn K, et al. Phase II single arm trial of aflibercept in patients with recurrent temozolomide-resistant glioblastoma: NABTC 0601 [abstr. #2020]. *J Clin Oncol*. 2008;26(suppl).

Cell

Clinical Application of Therapies Targeting VEGF

George D. Yancopoulos[1,*]
[1]Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591, USA
*Correspondence: george@regeneron.com
DOI 10.1016/j.cell.2010.09.028

This year's Lasker DeBakey Clinical Research Award goes to Napoleone Ferrara for the discovery of vascular endothelial growth factor (VEGF) as a major mediator of angiogenesis and for the development of an effective anti-VEGF therapy for wet macular degeneration, a leading cause of blindness in the elderly.

Many of us have been lured into a career in science by the hope that we would someday make a scientific discovery benefiting patients suffering from a previously incurable disease. Only as we progress in our careers do we realize how difficult and rare such a discovery is, not to mention how disconnected the actual scientific discovery often is from the development of a new therapeutic based on that discovery. Thus it is exceptionally rare that a single individual not only makes the seminal discovery but also helps to champion the development of an effective new class of therapeutics. Napoleone Ferrara, recipient of this year's Lasker DeBakey Clinical Reseach Award, provides a rare such example.

Ferrara's landmark scientific discovery involved the isolation and cDNA cloning of vascular endothelial growth factor (VEGF) as a mitogen for vascular endothelial cells. In large part due to Ferrara's subsequent efforts, we now know that VEGF is the most important driver in the body of normal as well as pathological blood vessel growth. We also now realize that VEGF not only induces vessel sprouting and growth but can also regulate vessel function in other ways, so as to regulate vascular tone and blood pressure, as well as vessel wall integrity and vascular permeability. The Lasker committee is recognizing Ferrara for the discovery of VEGF and for his specific contribution to the eye field, where he played a key role in the development of an anti-VEGF therapy for age-related macular degeneration (AMD), a leading cause of blindness in the elderly. Although not directly acknowledged in the current award, Ferrara made arguably even more exceptional contributions to the parallel development of a similar therapy for cancer.

Distinct Vascular Pathologies in Eye Diseases and in Cancer

The vasculature plays a critical role in a variety of eye diseases as well as in cancer growth. In AMD, the most severe vision loss occurs in patients who develop the "wet form" of the disease characterized by choroidal neovascularization (CNV). CNV refers to the growth of abnormal vessels originating from the choroidal vascular network, directly underlying the retina. The abnormal vessels do not usually invade the neural retina and thus do not directly disrupt the retina and its function. Instead, these abnormal vessels become excessively leaky, leading to retinal swelling and edema, which in turn impairs vision. Optical coherence tomography (OCT) can beautifully image the living retina and reveal the extent of swelling, including within the macula and its foveal region, the tiny central portion of the retina that is responsible for the "central vision" critical to important tasks such as reading and driving. OCT images demonstrate that patients with AMD can have marked swelling in their central retina to over three times normal thickness, resulting in severe vision loss (Figure 1).

As Ferrara himself has thoroughly reviewed, the observation that tumor growth is associated with increased vascularity was initially made over 100 years ago, and this observation was then followed by a series of classic papers over the following decades suggesting that tumors might produce a diffusible factor that stimulates angiogenesis, and that this angiogenesis could be required for tumor growth (Ferrara et al., 2004). The realization that the apparently disparate vascular pathologies in cancer and eye diseases had a common trigger, and thus potentially a related cure, awaited the discovery and cloning of VEGF.

The Discovery and Cloning of VEGF and VPF

In 1989, Ferrara and Henzel, working at Genentech, reported the purification and amino-terminal sequence of an endothelial-specific mitogen; they termed this protein VEGF. Shortly thereafter, Ferrara and colleagues described the molecular cloning of the cDNA encoding VEGF (Leung et al., 1989). While Ferrara and his colleagues focused on the endothelial growth properties of this new protein, a parallel effort was unknowingly trying to purify and clone the same protein, but with an eye toward a totally different biological function. In 1983, the Dvorak laboratory identified a tumor-derived factor, which they termed "vascular permeability factor" (VPF), that rapidly and potently induced microvascular permeability and fluid leak but for which they had no molecular sequence (Senger et al., 1983); I remember first hearing the VPF story directly from Dvorak in the mid-1980s at Cold Spring Harbor when he attended the cloning course that I was teaching, along with Fred Alt and Al Bothwell, in which Dvorak was trying to gain the expertise to clone this intriguing factor. Presumably because our training

of Dvorak was not sufficient, cloning of VPF was subsequently undertaken by the Monsanto Company, which published the amino-terminal protein sequence as well as the cDNA sequence in 1989 (Connolly et al., 1989; Keck, 1989).

Cloning of VEGF and VPF revealed that they were the same factor, and this convergence showed that this new factor had at least two fascinating biologic activities—not only could it induce endothelial cell proliferation, but it could cause vascular leak and edema. Over the next two decades, Ferrara was the clear world leader in further elucidating the biology and pathological roles of this new growth factor, helping drive more widespread adoption of VEGF as its name. Ferrara early on realized the value of using genetic inactivation in mice, as well as engineered biologics that could work in multiple species, as powerful tools. In 1996, he demonstrated that early mouse development depended on precise dosing of VEGF by showing that inactivation of even a single VEGF allele resulted in embryonic lethality due to severe vascular abnormalities. He cleverly developed and elegantly exploited biologics-based blockers (such as antibodies and soluble receptors) to show that VEGF is required for overall postnatal growth, and to define its roles in structures such as growing bones and the cycling ovary (Gerber et al., 1999a, 1999b). He also worked with collaborators to show that VEGF acted via an endothelial-specific receptor tyrosine kinase, further confirming that evolution had selected VEGF to act specifically on the vascular endothelium by limiting its receptor distribution to these cells.

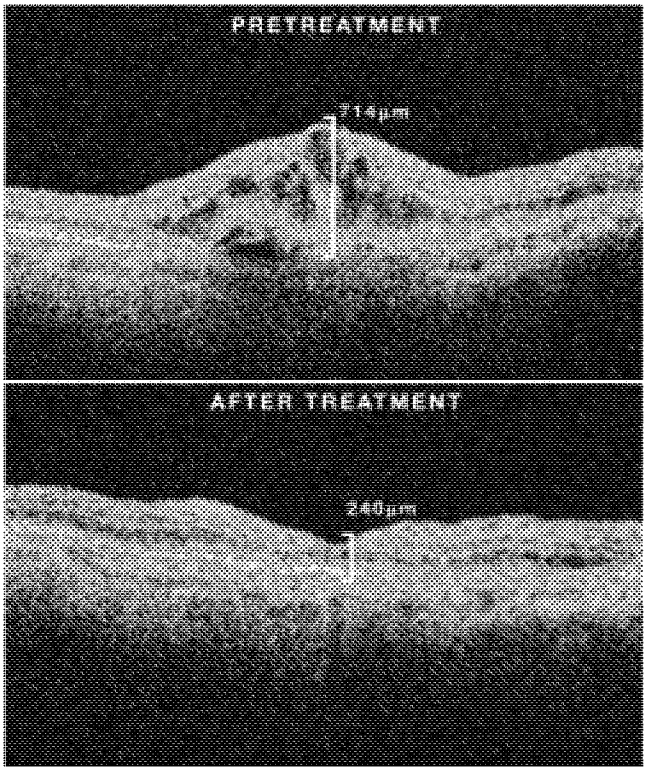


Figure 1. Anti-VEGF Therapy for Wet Age-Related Macular Degeneration

Swelling of the central retina in a patient with age-related macular degeneration, as seen by optical coherence tomography, is reduced by treatment with anti-VEGF therapy. Prior to treatment this individual could read 35 letters on a specialized "ETDRS" eye chart. After treatment, this improved to 66.

VEGF and Tumor Angiogenesis

As noted above, it had long been appreciated that neo-angiogenesis accompanies and might be required for tumor growth. Building on this background, Folkman was the first to propose that therapies designed to prevent such angiogenesis might provide a useful new way to combat cancer (Folkman, 1971). Folkman, however, also presented a rather complicated view of tumor angiogenesis in which there were myriad positive and negative regulators, almost all of which (such as fibroblast growth factors, transforming growth factors, collagen fragments known as endostatin, and plasminogen fragments known as angiostatin) served roles outside of the vasculature as well; Folkman suggested that tumor angiogenesis depended on a complex integration of these various positive and negative regulators but did not propose a specific angiogenic pathway nor a key trigger. In contrast, Ferrara showed that angiogenesis depended on a clear cascade of factors, with VEGF as the key initiator of most angiogenic processes; Ferrara's demonstration of the primacy of VEGF also pushed the field to realize that additional growth factors had also evolved to specifically regulate the endothelium by similarly utilizing endothelial-specific receptors, such as other members of the VEGF family as well as the more recently discovered angiopoietin family (Yancopoulos et al., 2000).

Diligently pursuing his focus on VEGF, Ferrara developed a mouse monoclonal antibody to block VEGF, termed A.4.6.1. It was initial experiments using this antibody in animal models that established the primacy of VEGF in tumor angiogenesis—Ferrara showed that the antibody could strongly inhibit tumor growth by limiting tumor-induced angiogenesis, not only providing the first convincing evidence that blocking tumor angiogenesis could indeed prevent tumor growth but simultaneously establishing VEGF as the critical target in the process (Kim et al., 1993); importantly, the results were reproduced in many laboratories using an assortment of VEGF-blocking reagents, including a clinical candidate termed the VEGF Trap that was developed in our laboratory.

Despite the results with VEGF blockade reported by Ferrara and others, the pharmaceutical industry did not immediately jump on VEGF as an exciting cancer target. In part, this had to do with prevailing views in the field that there were myriad potential targets to attack, and that no target was more important than others. Ferrara pressed on and next humanized A.4.6.1 so that it could be used in human trials. This humanized antibody, given the generic name bevacizumab and the brand name Avastin, first entered clinical trials in 1997. Bevacizumab ultimately achieved FDA approval in 2004 as a first-line treatment for metastatic colorectal cancer in combination with chemotherapy, based on its statistically and clinically meaningful benefits on progression-free survival and overall survival (Ferrara et al., 2004), and has since garnered additional approvals. The

bevacizumab story provides the definitive demonstration that, in man, specific antiangiogenesis blockade can provide useful tumor control in multiple cancer settings and is a testimonial to the efforts and persistence of Ferrara, and it still remains the standard for angiogenesis-based therapeutics.

Kinase inhibitors that target the VEGF receptor signaling pathway have since been approved in cancer but do not display as widespread activity while also exhibiting broader toxicities. There appear to be several reasons for this. Biologics-based therapies such as bevacizumab are naturally selected to have high affinity and great specificity for their target and also have the benefit of long-circulating half-lives following injection, allowing for rather complete and long-term blockade with little if any off-target activity, which has proven more difficult to achieve with small-molecule kinase inhibitors. Probably due to the confusion that marked the field a few years ago, few biologics-based VEGF-targeted therapies are in late-stage clinical trials in cancer; it remains to be seen whether either of the two biologicals in phase III trials (that is, the VEGF Trap or Lilly's ramucirumab that targets the VEGF receptor) will provide similar or even greater benefit than bevacizumab.

Anti-VEGF Therapy for Eye Diseases

Ferrara played a key role in the development of anti-VEGF therapies for eye diseases, an endeavor that depended on the contributions and influence of several key collaborators as well as independent groups. First of all, it should be pointed out that most believe it is the permeability-inducing activity of VEGF, first described by Dvorak, that leads to the retinal swelling and edema that cause vision loss in wet AMD; other eye diseases (such as proliferative diabetic retinopathy) do exhibit the profound pathologic neovascularization that we now know is also driven by VEGF. It was in the latter type of settings that the first definitive link between VEGF and human eye disease was made, simultaneously in 1994 by Adamis and colleagues as well as Aiello and King working in collaboration with Ferrara (Adamis et al., 1994; Aiello et al., 1994); both groups showed marked increases in VEGF levels in the eyes of patients suffering from intraocular neovascularization. Shortly thereafter, both groups worked in collaboration with Ferrara to show the benefit of blocking VEGF in animal models of ocular neovascularization; Ferrara provided the critically required anti-VEGF blocking reagents for these seminal studies.

The introduction of anti-VEGF therapies into the clinic for eye diseases came from a completely unexpected source, a small company named NeXstar Pharmaceuticals. This company was based on Larry Gold's "aptamer" technology, which was being used to develop small synthetic RNAs as a new class of drugs, and one of their scientists, Nebojsa Janjic, was developing an anti-VEGF aptamer with cancer in mind; however, this aptamer was ineffective when systemically administered in animal tumor models. Stimulated by Adamis' paper, Janjic reasoned that his aptamer might work better if directly injected into the eye. Toward this end, Janjic met in 1996 with Adamis and Guyer, who helped Janjic design a clinical development plan for AMD. The aptamer, termed Macugen, entered clinical trials in 1999. In the meantime, Adamis and Guyer decided to try to start their own venture and searched for the best available VEGF inhibitor they could license for use in the eye; it was at this point that I met the pair as they became interested in our VEGF Trap, and I became convinced by their compelling rationale. Unfortunately, the VEGF Trap was then entangled in a collaboration with the Proctor & Gamble Health Care group, which was not interested in either developing it or out-licensing it for the eye, and thus Adamis and Guyer had to look elsewhere; several years later, we were independently able to progress the VEGF Trap into the clinic for eye diseases. By 2000, Adamis and Guyer had started a company called Eyetech and, not having other options, licensed Macugen and continued its clinical development. In phase III, Macugen produced rather modest results, somewhat slowing the progressive visual decline of AMD but was nevertheless approved by the FDA in 2004; Pfizer entered into the mix and paid a huge premium to obtain rights to this innovative therapeutic.

Although temporally behind the Macugen story, and certainly spurred by the competition, Ferrara and Genentech had far superior VEGF blockers at their disposal. Because of concerns that a full-length antibody might not diffuse efficiently into the retina when injected into the vitreous, Ferrara and his colleagues decided to engineer a humanized Fab variant of A.4.6.1 for use in the eye that was ultimately given the generic name ranibizumab and the brand name Lucentis (Ferrara et al., 2006). Ranibizumab had other advantages over bevacizumab, most notably a much higher affinity that allowed it to be active at lower concentrations, which Ferrara felt might be important in terms of allowing for maintained activity when the drug would drop to low levels between monthly injections into the eye. Genentech initially dosed patients with ranibizumab in 2000 and received FDA approval for the treatment of wet AMD in 2006. The efficacy results were quite stunning, especially when compared to those obtained with the poorer blocker, Macugen. Instead of merely slowing vision loss, patients on average gained vision and maintained these gains if dosed on a monthly schedule. Ranibizumab has since been studied in other eye diseases and recently gained approval for retinal vein occlusion. Worldwide, Lucentis is now being used to treat about a quarter million patients a year. It perfectly fits the definition of pharmaceutical blockbuster, in terms of providing enormous clinical benefit to many patients while simultaneously producing enormous revenues. However, there are emerging issues. In part frustrated by the cost of ranibizumab, clinicians explored off-label use of intravitreal injection of bevacizumab for eye diseases and claimed to see similar benefit (Rosenfeld, 2006). While there are certainly concerns in terms of safety risks to patients of such off-label use, the National Eye Institute decided that the potential pharmacoeconomic value of a lower-priced alternative warranted running clinical trials directly comparing ranibizumab and bevacizumab in AMD; results are expected in 2011. In addition, because patients and physicians are very interested in decreasing the frequency of eye injections, there have been many attempts to study less frequent dosing paradigms; despite these efforts, current evidence supports the need for regular if

not monthly injection of ranibizumab to optimize its benefit. Early studies with other biologics blockers raise the possibility that an even higher-affinity blocker, perhaps at higher doses, could provide further visual gains or allow for longer interval dosing.

In many ways, Ferrara's career represents the fulfillment of every drug discoverer's dream, and the Lasker Award could not be going to a more worthy recipient. Ferrara not only made a seminal scientific discovery, but then he and his colleagues at Genentech built on this discovery to spearhead the development of an entirely new class of therapeutics with major applications in two previously distinct clinical arenas—vascular eye diseases and cancer. Although Ferrara's VEGF antibody is now being used to treat about 250,000 cancer patients a year, the current award may have avoided specifically acknowledging Ferrara's contribution to the cancer field because of questions regarding the degree of clinical benefit of bevacizumab in cancer. Because bevacizumab represents an entirely new way of attacking cancer, utilization of this approach is still a work in progress and may require new treatment paradigms to optimize benefit. Traditional treatment paradigms in which the anticancer therapy is stopped after a short treatment period when tumor killing is thought to be completed, or after tumor progression when the tumor is thought to have become chemo-resistant, make little sense for an antiangiogenesis approach: the point is not to try to wipe out the tumor initially but instead to provide ongoing control by limiting host support; any benefit would be expected to dissipate as soon as such therapy is stopped. Ferrara's colleagues at Genentech have nicely demonstrated this point in very recent animal studies (Bagri et al., 2010), as well as in recent clinical studies including one in ovarian cancer using an innovative "maintenance design" carried out by the Gynecological Oncology Group (GOG-0218). Data from this study can be used to make several important points. First, this study shows that, at least in this setting, bevacizumab does not primarily work by allowing more efficient delivery of chemotherapy (as had been proposed by others), given that the gained benefit is at least as good during the monotherapy maintenance stage as during the prior combination stage. Moreover, the study convincingly shows that continued maintenance with anti-VEGF therapy is necessary to prevent loss of clinical benefit. In addition to maintenance approaches or treatment-through-progression strategies, the benefit of anti-VEGF therapy may also be improved by combining with agents targeting other angiogenic pathways; notably, several companies are in trials combining anti-VEGF agents with other antiangiogenic agents, such as those targeting Angiopoietin-2. Chemotherapeutics may also be developed that work better on tumors made hypoxic via antiangiogenic therapy. Although antiangiogenesis approaches in cancer are likely to be further optimized as the community learns better how to take advantage of this approach, there is little doubt that anti-VEGF treatments pioneered by Ferrara and his colleagues will long remain the foundation of such efforts. Thus, it can be hoped that this well-deserved Lasker award for the discovery of VEGF and the development of a treatment for AMD is a harbinger of prestigious accolades to come that would also include specific recognition of Ferrara's contributions to tumor biology and cancer treatment.

ACKNOWLEDGMENTS

G.D.Y. works at Regeneron, which is developing anti-VEGF therapeutics.

REFERENCES

Adamis, A.P., Miller, J.W., Bernal, M.T., D'Amico, D.J., Folkman, J., Yeo, T.K., and Yeo, K.T. (1994). Am. J. Ophthalmol. *118*, 445–450.

Aiello, L.P., Avery, R.L., Arrigg, P.G., Keyt, B.A., Jampel, H.D., Shah, S.T., Pasquale, L.R., Thieme, H., Iwamoto, M.A., Park, J.E., et al. (1994). N. Engl. J. Med. *331*, 1480–1487.

Bagri, A., Berry, L., Gunter, B., Singh, M., Kasman, I., Damico, L.A., Xiang, H., Schmidt, M., Fuh, G., Hollister, B., et al. (2010). Clin. Cancer Res. *16*, 3887–3900.

Connolly, D.T., Olander, J.V., Heuvelman, D., Nelson, R., Monsell, R., Siegel, N., Haymore, B.L., Leimgruber, R., and Feder, J. (1989). J. Biol. Chem. *264*, 20017–20024.

Folkman, J. (1971). N. Engl. J. Med. *285*, 1182–1186.

Ferrara, N., Hillan, K.J., Gerber, H.-P., and Novotny, W. (2004). Nat. Rev. Drug Discov. *3*, 391–400.

Ferrara, N., Damico, L., Shams, N., Lowman, H., and Kim, R. (2006). Retina *26*, 859–870.

Gerber, H.P., Hillan, K.J., Ryan, A.M., Kowalski, J., Keller, G.A., Rangell, L., Wright, B.D., Radtke, F., Aguet, M., and Ferrara, N. (1999a). Development *126*, 1149–1159.

Gerber, H.P., Vu, T.H., Ryan, A.M., Kowalski, J., Werb, Z., and Ferrara, N. (1999b). Nat. Med. *5*, 623–628.

Keck, P.J. (1989). Science *246*, 1309–1312.

Kim, K.J., Li, B., Winer, J., Armanini, M., Gillett, N., Phillips, H.S., and Ferrara, N. (1993). Nature *362*, 841–844.

Leung, D.W., Cachianes, G., Kuang, W.J., Goeddel, D.V., and Ferrara, N. (1989). Science *246*, 1306–1309.

Rosenfeld, P.J. (2006). Am. J. Ophthalmol. *142*, 141–143.

Senger, D., Galli, S., Dvorak, A., Perruzzi, C., Harvey, V., and Dvorak, H. (1983). Science *219*, 983–985.

Yancopoulos, G.D., Davis, S., Gale, N.W., Rudge, J.S., Wiegand, S.J., and Holash, J. (2000). Nature *407*, 242–248.

REGENERON

Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration

May 8, 2008

Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration**Leverkusen, Germany, Montville, NJ and Tarrytown, NY, May 8, 2008 -** Bayer HealthCare AG and Regeneron Pharmaceuticals, Inc. (NASDAQ:REGN) today announced that the first patient has been dosed in the VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of the neovascular form of Age-related Macular Degeneration (wet AMD), a leading cause of blindness in adults.

VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) will enroll approximately 1,200 patients in up to 200 centers in Europe, Asia Pacific, Japan and Latin America. The first Phase 3 trial, VIEW 1, began enrolling patients in August 2007 in the United States and Canada. Both VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks. The development program will include visual acuity endpoints and anatomical endpoints, including retinal thickness, a measure of disease activity. The trial is intended to establish non-inferiority of VEGF Trap-Eye with Lucentis®* (ranibizumab), an antiangiogenic agent approved for use in wet AMD in major markets globally.

Wet AMD accounts for about 90 percent of all severe AMD-related vision loss. It occurs when abnormal blood vessels in the eye leak fluid and blood into the macula, the area of the retina that allows for vision of fine details. This can lead to a rapid loss of central vision with continued progression.

"Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision," said Kemal Malik, MD, Head of Global Development and member of the Bayer HealthCare Executive Committee. "Dosing of the first patient in this confirmatory Phase 3 trial is an important milestone for this compound intended to treat a devastating ocular disease that impacts millions of people worldwide."

"New therapies are still needed to provide optimal care to those patients with wet AMD," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "This global Phase 3 clinical program will provide additional data to further evaluate the efficacy and safety of VEGF Trap- Eye using different dosing regimens."

Bayer HealthCare and Regeneron are collaborating on the global development of VEGF Trap-Eye for treatment of wet AMD, diabetic eye diseases, and other ocular diseases and disorders. Once approved, Bayer HealthCare will market VEGF Trap-Eye outside the U.S., where the parties will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the U.S. VIEW 2 primary analysis results are anticipated in 2011.

About VIEW 2

In the first year, the VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every 4 weeks. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but not more often than every 4 weeks until the end of the study.

The primary endpoint of the study is the proportion of patients treated with VEGF Trap-Eye who maintain vision at the end of one year, compared to ranibizumab patients. Visual acuity is defined as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, a standard chart used in research to measure visual acuity. Maintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart. Key secondary endpoints include the mean change from baseline in visual acuity as measured by ETDRS and the proportion of patients who gained at least 15 letters of vision at week 52.

Phase 2 Clinical Data

In a Phase 2 trial in 157 patients, announced in October 2007 at the Retina Society Conference in Boston, VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart).

Following the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN (as needed) dosing schedule based upon the physician assessment of the need for re-treatment in accordance with pre-specified criteria. At the 2008 meeting of the Association for Vision and Ophthalmology (ARVO), it was reported that, on average, patients on the PRN dosing schedule maintained the gain in visual acuity and decrease in retinal thickness achieved at week 12 through week 32 of the study.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger the formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye, which lead to the development of wet AMD. VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PlGF) and VEGF-B. VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. Blockade of VEGF can prevent abnormal blood vessel formation as well as vascular leak and has proven beneficial in the

treatment of wet AMD.

About Wet AMD

Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subsidiary of Bayer AG, is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Diabetes Care and Pharmaceuticals divisions. The pharmaceuticals business operates under the name Bayer Schering Pharma AG. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Find more information at www.bayerhealthcare.com. Bayer Schering Pharma is a worldwide leading specialty pharmaceutical company. Its research and business activities are focused on the following areas: Diagnostic Imaging, General Medicine, Specialty Medicine and Women's Healthcare. With innovative products, Bayer Schering Pharma aims for leading positions in specialized markets worldwide. Using new ideas, Bayer Schering Pharma aims to make a contribution to medical progress and strives to improve the quality of life. Find more information at www.bayerscheringpharma.de.

About Regeneron

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST™ (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, and inflammatory diseases, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's Web site at www.regeneron.com.

*(Note: Lucentis® is a registered trademark of Genentech, Inc.)

Contact at Bayer HealthCare:
Astrid Kranz, Phone: +49 30 468 12057
E-mail: astrid.kranz@bayerhealthcare.com
Rose Talarico, Phone: +1 973 305 5258
E-mail: rose.talarico@bayer.com
Contact at Regeneron:
Laura Lindsay, Phone: +1 914 345 7800
E-mail: laura.lindsay@regeneron.com
Lauren Tortorete, Phone: +1 212 845 5609
E-mail: ltortorete@biosector2.com
AK (2008-0144E)

Bayer HealthCare Forward Looking Statement

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Regeneron Forward Looking Statement

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-Q for the quarter ended March 31, 2008. Regeneron does not undertake any obligation to update publicly any forwardlooking statement, whether as a result of new information, future events, or otherwise unless required by law.

Clinical Ophthalmology

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Retinal vein occlusion: pathophysiology and treatment options

Niral Karia

Department of Ophthalmology, Southend Hospital, Prittlewell Chase, Westcliff on Sea, Essex, United Kingdom

Abstract: This paper reviews the current thinking about retinal vein occlusion. It gives an overview of its pathophysiology and discusses the evidence behind the various established and emerging treatment paradigms.

Keywords: central, hemispheric, branch, retinal vein occlusion, visual loss

Introduction

Retinal vein occlusion (RVO) is the most common retinal vascular disease after diabetic retinopathy.[1] Depending on the area of retinal venous drainage effectively occluded it is broadly classified as either central retinal vein occlusion (CRVO), hemispheric retinal vein occlusion (HRVO), or branch retinal vein occlusion (BRVO). Hayreh observed that each of these has two subtypes.[2] The former two can be subdivided into ischemic and nonischemic CRVO or HRVO, with each having distinct clinical features and prognosis. A number of parameters can be used to assess the degree of ischemia such as the degree of visual loss, presence of a relative afferent pupillary defect, extent of retinal capillary nonperfusion on fluorescein angiography, and electrodiagnostics showing reduced b wave amplitude, reduced b:a ratio and prolonged b-wave implicit time.

BRVO can be considered a major BRVO where a quarter or more of the retina is affected or a macular BRVO where only part of the macular is affected.

Presentation of RVO in general is with variable painless visual loss with any combination of fundal findings consisting of retinal vascular tortuosity, retinal hemorrhages (blot and flame shaped), cotton wool spots, optic disc swelling and macular edema. In a CRVO, retinal hemorrhages will be found in all four quadrants of the fundus, whilst these are restricted to either the superior or inferior fundal hemisphere in a HRVO. In a BRVO, hemorrhages are largely localized to the area drained by the occluded branch retinal vein. Vision loss occurs secondary to macular edema or ischemia.

Epidemiology

The true incidence of RVO in a population as a whole is difficult to establish, as many RVOs are silent where the condition is mild, the patient is asymptomatic, and it is only detected incidentally. However, longitudinal population based studies have helped in providing an estimate of this incidence. The Blue Mountains Eye Study[1] found that the 10-year cumulative incidence of RVO was 1.6% and was significantly associated with increasing age, especially over the age of 70 years. However there was

Correspondence: Niral Karia
Department of Ophthalmology, Southend Hospital, Prittlewell Chase, Westcliff on Sea, Essex SS00RY, United Kingdom
Tel +44 1702 435 555
Fax +44 1702 385 877
Email niral.karia@southend.nhs.uk

no predilection for gender or race.[3] The Beaver Dam Eye Study[4] reported a 15-year cumulative incidence of CRVO of 0.5%. For a BRVO this was approximately three times more at 1.8%. Applying this to United Nations projected UK population figures for 2010 gives approximately 47,000 new cases annually.[5] This figure is greater than 150,000 for the United States.[6] Rogers et al[7] carried out a pooled analysis of population based studies from the United States, Europe, Asia, and Australia and projected that approximately 16 million people worldwide may have RVO in at least one eye worldwide. The pooled data showed a higher prevalence of BRVO in Asians and Hispanics compared to whites, although this was not statistically significant, and there was no gender predilection. Whilst less common, it is now generally accepted that (idiopathic) RVO does also occur in the younger (under 50 years) age group, where CRVO tends to be more of the nonischemic type.[2]

Etiology

Although the exact etiology of RVO remains elusive, it is likely to follow a thrombotic event. In CRVO this may occur in the central retinal vein (CRV) at the lamina cribrosa[8] or at a variable distance in its journey within the optic nerve posterior to the lamina cribrosa. A more posterior occlusion with a greater number of tributaries of the CRV anterior to the occlusion may allow greater scope for collateral flow to bypass the occluded section of the CRV.[2] In BRVO, arterial compression of the vein at arteriovenous crossings is thought to incite thrombus formation by causing turbulent flow in combination with pre-existing vascular endothelial damage secondary to systemic cardiovascular risk factors.

In trying to determine etiology or associated risk factors for RVO, comparison is naturally made to factors involved in the occurrence of systemic venous thrombosis (such as deep vein thrombosis). Whilst these two entities may share some common cardiovascular and systemic risk factors, it is also important to understand that they are otherwise quite separate entities requiring different management strategies and leading to different complications.[2]

Systemic vascular/atherosclerotic risk factors in RVO

Study design, patient characteristics, and risk factor definitions are seldom standardized across the various published papers in the literature. However accounting for this it remains probable that systemic hypertension is the strongest independent risk factor associated with all types of RVO[9–13] especially in the older (over 50 years) age group. Uncontrolled or newly diagnosed hypertension is common in this group, and recurrence of RVO in the same or fellow eye is also noted when hypertension is poorly controlled. In their meta-analysis of 21 studies, O'Mahoney et al[12] report a significant association between hypertension and both CRVO (pooled odds ratio [OR = 3.8] and BRVO [pooled OR 3.0]. Accepting an inconsistent definition of hyperlipidemia across studies they also found hyperlipidemia to be twice as common in RVO cases (both CRVO and BRVO) compared to controls (pooled OR 2.5). Cheung et al[3] also report hypertension and hyperlipidemia as independent risk factors for RVO. The association of diabetes mellitus with RVO is weaker and has not been found to be consistent across all studies.[12] Its association with CRVO may be stronger than with BRVO.[9,12,13]

Hematological disorders and other systemic conditions

Conditions that lead to increased blood viscosity such as myeloproliferative disorders are uncommon but known to be associated with CRVO. Similarly, a number of rare systemic inflammatory disorders causing systemic vasculitis (such as Behçet's disease and polyarteritis nodosa) also cause retinal vasculitis leading to RVO, especially in the younger age group. The cause and management of the RVO here is closely linked to the underlying systemic disease and its management.

Over recent years there has been great interest in the potential role of thrombophilia in the development of RVO and in particular CRVO. Thrombophilia refers to the propensity to develop thrombosis (usually venous) due to an abnormality in the coagulation system. This can be congenital (eg, Factor V Leiden, hyperhomocysteinemia or protein C, protein S and antithrombin deficiencies) or acquired (eg, antiphospholipid syndrome), and its importance is potentially greater in the younger age group. However Fegan's review on CRVO and thrombophilia[14] suggested that there was a lack of consistency between studies in showing a valid association between CRVO and protein C, protein S and antithrombin III deficiency, and factor V Leiden/activated protein C resistance. These natural anticoagulants are very labile with fluctuating physiological levels. It is recommended that they should be measured on at least two separate samples and if found abnormal confirmed with a third estimation. Most studies used single measurements and varying types of assays. The studies also lacked the statistical power to show a true difference either due to small sample size or lack of a suitable control group.

In the antiphospholipid syndrome (APS) antibodies to phospholipid activate the coagulation cascade leading to both arterial and venous thrombosis. Tests can be done to either detect the antibody (using the anticardiolipin antibody assay) or its effect on coagulation using a test for lupus anticoagulant. Up to 8% of patients with APS have ocular manifestations and 4 of 8 studies reviewed by Fegan[14] showed a significant association of APS in CRVO. Further studies are required to determine the strength of association between APS and RVO.

Homocysteine is a naturally occurring amino acid not found in protein. There are many causes for hyperhomocysteinemia (including rare enzyme deficiencies leading to homocystinuria) which predisposes to both arterial and venous thrombosis.[14] Several studies have questioned the validity of carrying out exhaustive tests for thrombophilia in RVO in the absence of a suggestive medical history. However their results have shown notable evidence of an association of hyperhomocysteinemia with CRVO sufficient to recommend the benefit of checking for hyperhomocysteinemia, which is correctable with folic acid and vitamins B6 and B12 supplements.[14–17]

On current evidence it would be reasonable to not recommend general thrombophilia screening for all patients with RVO, but to reserve it for older patients with a past history of thromboembolic events and in young patients without any other general risk factors.

Glaucoma/ocular hypertension

The association between RVO (CRVO in particular) and glaucoma/ocular hypertension has been widely reported[2,9,11,13,18] with the Eye Disease Case-Control Study[9] reporting an adjusted OR of 5.4 in CRVO for a history of glaucoma. The pathophysiology of this association is unclear, although deformation of the lamina cribrosa in glaucoma may distort the central retinal vein as it exits the eye.

Familial RVO

Familial clustering of RVO (CRVO in particular) has been reported[19,20] but these reports have been few in number. It is interesting that such cases are more often bilateral, with a younger age at onset than sporadic cases. More data from existing and future familial clusters is required to establish if there is a genetic cause in these cases.

Pathophysiology of RVO

It is the occurrence of macular edema in retinal vein occlusion that most frequently leads to visual loss. A working understanding of the pathogenesis of the macular edema may in turn allow an understanding of the mechanism of action of some of the therapies more recently advocated in retinal vein occlusion.

Thrombosis within a retinal vein as described earlier will lead to a partial obstruction of blood flow within the vein and from the eye. The subsequent increased intraluminal pressure, if sufficiently high, will cause transudation of blood products into the retina according to Starling's law. This will result in increased interstitial (retinal) fluid and protein. The latter will increase the interstitial oncotic pressure, perpetuating tissue edema, which will impede capillary perfusion and lead to ischemia. As stated by Campochiaro et al[21] this ischemia is not an all or none dichotomy, as those patients classified as nonischemic will still have varying degrees of retinal ischemia.

It is well recognized that inflammation affects the progression and outcome of vitreoretinal disease including retinal vein occlusion.[22] Yoshimura et al[22] have found significantly elevated vitreous levels of the soluble cytokines interleukin (IL) 6 and 8, monocyte chemoattractant protein-1, and vascular endothelial growth factor (VEGF) in RVO, and especially in CRVO. Funk et al[23] have also demonstrated elevated aqueous levels of these same factors in patients with CRVO when compared with control samples. The exact interaction of these factors remains speculative but an understanding of the roles that VEGF fulfils is increasing. It is induced by tissue hypoxia such as retinal ischemia and acts as an angiogenic and vasopermeable factor on endothelial cell membrane bound receptors with tyrosine kinase activity.[24] Ozaki et al[25] have demonstrated that the implantation of slow release pellets of human recombinant VEGF into the vitreous cavity of rabbits and primates leads to retinal vessel dilatation, breakdown of the blood retinal barrier and retinal new vessel formation. Noma et al have reported elevated aqueous and vitreous levels of VEGF and IL-6 in patients with BRVO[26,27] and CRVO,[28,29] compared to controls. The levels of VEGF and IL-6 correlated with both the severity of macular edema and extent of retinal ischemia (capillary nonperfusion).

It is likely that the sudden retinal ischemia that occurs in BRVO and more so in CRVO will induce excessive VEGF production. VEGF is produced by the retina from retinal pigment epithelial cells, endothelial cells, and Muller cells, as well as other types of ocular tissue.[22] Boyd et al found a close correlation between aqueous VEGF levels and the course of iris neovascularization and vascular permeability in patients with ischemic CRVO.[30] The excessive vascular permeability induced by VEGF will likely contribute to the

macular edema that also occurs according to Starling's law as described above. It is tempting to theorize that even if the primary venous obstruction was overcome (eg, via collateral formation), the macular edema can persist for much longer due to a self perpetuating cycle of VEGF-induced vascular permeability leading to macular edema, capillary damage, and retinal ischemia, stimulating further release of VEGF and other inflammatory cytokines leading to chronic macula edema.

Treatment

The Branch Retinal Vein Occlusion Study (BRVOS)[31,32] and the Central Retinal Vein Occlusion Study (CRVOS)[33,34] have established a standard of care by providing both an understanding of the natural history and treatment algorithms for BRVO and CRVO in managing neovascular complications and reducing visual loss. The studies were designed to answer specific questions and so have inherent limitations. Whilst many aspects of these studies may now arguably seem dated, some remain pertinent. In their review of studies evaluating the natural history of CRVO Rogers et al[35] confirm that eyes with CRVO had generally poor vision at presentation which declined further with time. They found that over a quarter of nonischemic CRVO converted to ischemic CRVO, of which a quarter developed neovascular glaucoma within 15 months. Similarly they reviewed studies evaluating the natural history of BRVO and reported a general improvement in vision over time without treatment, although improvement beyond 20/40 was uncommon.

Therapeutic options for CRVO

Mohamed et al[36] carried out a systematic review of randomized clinical trials (RCTs) evaluating interventions for the treatment of CRVO. Only results from the CRVOS[33,34] met the criteria for level 1 evidence. In patients with macular edema secondary to nonischemic CRVO with a vision of 20/50 or worse, macular grid laser photocoagulation does not improve visual acuity although the edema may improve. Additionally prophylactic pan retinal photocoagulation (PRP) in ischemic CRVO does not prevent iris or angle neovascularization and is therefore not recommended. PRP is recommended when anterior segment, disc or retinal neovascularization develop.

Mohamed et al[36] also evaluated studies reporting on hemodilution, medical treatment with troxerutin and ticlopidine (inhibitors of platelet aggregation) and intravenous thrombolysis, and various surgical procedures to improve vision in CRVO. By lowering the hematocrit, and thus the plasma viscosity, hemodilution is thought to improve the retinal microcirculation. However the variations in study protocols and the use of multiple agents in combination have prevented any conclusions to be drawn for this treatment modality. Similarly there is limited evidence to recommend the routine use of troxerutin or ticlopidine as well for intravenous thrombolysis, which carries the potential for serious adverse effects such as stroke. The reviews by Squizzato et al[37] and Lazo-Langner et al[38] suggest that antithrombotic therapy, with low molecular weight heparin (LMWH) in particular, may be efficacious in the treatment of acute RVO with superiority over antiplatelet agents such as aspirin. LMWH appear to have additional properties such as anti-angiogenic effects, which may explain their additional benefits compared to other agents. However the limited evidence available precludes any recommendations about the use of LMWH.

Following a vitrectomy approach, several surgical procedures including internal limiting membrane peel,[39] radial optic neurotomy,[40,41] and direct retinal vein cannulation with injection of fibrinolytics,[42,43] have all been advocated for the management of macular edema in CRVO. However the mechanism of action of these interventions remains contentious and their safety and efficacy have not been evaluated in RCTs. Furthermore carrying out a vitrectomy in itself is thought to improve retinal oxygenation, so confounding the possible effects of the other procedures. Mohamed et al therefore conclude that the routine use of these procedures cannot be recommended.

McAllister et al[44] have reported the outcome of the first prospective randomized multicenter trial comparing laser-induced chorioretinal venous anastomosis (L-CRA) with conventional treatment (observation) for CRVO. This technique utilized a high power (argon or Nd:YAG) laser spot to rupture Bruch's membrane and a second spot to rupture a major branch of the retinal vein next to the first laser spot, the intention being to enable an anastomosis to form between the retinal and choroidal circulation. They were able to create a L-CRA in 76.4% of patients in whom an attempt was made, leading to a significant reduction in the mean retinal fluorescein transit time at 18 months in the treatment group compared to the controls. A mean improvement of 3.6 letters was seen in the treatment group that developed a L-CRA at 18 months compared to a loss of 8.1 letters from baseline in the control group. Although fewer eyes converted to ischemic CRVO in the treatment group compared to controls, 18.2% of treated eyes developed choroidal neovascularization (CNV) at the treatment site necessitating sector PRP. It remains to be seen whether

L-CRA becomes widely employed as a treatment option for CRVO. Although the technique is relatively noninvasive and readily accessible it does have a significant learning curve and a high potential rate of complication from CNV.

Therapeutic options for BRVO

The BRVOS[31] evaluated whether grid macular laser photocoagulation improved visual acuity (VA) in patients with VA of 20/40 or worse resulting from macular edema secondary to BRVO following at least 3 months of observation. McIntosh et al[45] conducted a literature search to identify all relevant RCTs evaluating interventions for BRVO. They concluded that only the results of the BRVOS[31] met criteria for level 1 evidence – patients treated with grid macular laser gained an average of 1.33 lines at the third year study visit from baseline compared with 0.23 lines in the control group. The grid laser group had statistically significant improvements in VA compared to controls over consecutive visits. Arnarsson and Stefansson[46] have postulated that destruction of photoreceptors by grid laser leads to increased oxygen flux to the inner retina. An autoregulatory arteriolar constriction and increased resistance then leads to reduced hydrostatic pressure in capillaries and venules, leading to reduced edema with vessel constriction and shortening.

Accepting methodological limitations (such as small sample sizes with insufficient power, short follow up, and lack of a control group), McIntosh et al[45] also evaluated studies reporting other interventions including hemodilution, surgery involving pars plana vitrectomy and adventitial sheathotomy, and medical treatment with ticlopidine and troxerutin. They found that these studies lacked sufficient evidence to support the routine use of these other treatment modalities. Muqit et al[47] recently reported on the long term vascular perfusion following arteriovenous sheathotomy for BRVO. In their small series they found that long-term epiretinal gliosis and subfoveal photoreceptor atrophy limited the visual recovery.

Intravitreal corticosteroids

With increasing awareness of the role of VEGF and other inflammatory mediators, the use of off label intravitreal corticosteroids (triamcinolone acetonide in particular) has become routine in the management of RVO in spite of a paucity of RCTs. Small scale studies have reported a positive short/intermediate term efficacy of intravitreal triamcinolone (IVT)[48,49] but Patel et al[50] found that whilst IVT was effective in the short term in treating macular edema secondary to all types of RVO, its effectiveness was not maintained after 1 year despite repeated injections.

The exact mechanism of action of corticosteroids in the resolution of macular edema remains speculative. Miyamoto et al[51] describe cases where macular edema from RVO or diabetic maculopathy had begun to resolve within 1–6 hours of injecting IVT. They proposed that in addition to the recognized genomic pathway whereby receptor-glucocorticoid interaction is translocated to the nucleus leading to regulation of gene expression and taking many hours or days, there is also a nongenomic pathway. Here the receptor-glucocorticoid complex may act within the cytoplasm to destabilize mRNA, such as VEGF messengers, with rapid effects.

The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) studies[52,53] reported RCT data on the efficacy of 1mg and 4 mg of a preservative free, nondispersive formulation of triamcinolone injected intravitreally. This was compared to the standard of care – observation for macular edema in CRVO[52] and grid laser photocoagulation for macular edema in BRVO.[53] Whilst the SCORE studies have several methodological limitations, as discussed by Apte in his editorial,[54] they provide important information that modifies the standard of care established by the BRVOS[31,32] and CRVOS.[33,34] The SCORE-BRVO study[53] reported that at the 12 month end point there were no significant differences in visual acuity between the laser treatment, 1 mg and 4 mg groups. The SCORE-CRVO study[52] however found that subjects in the 1 mg and 4 mg arms were five times more likely to show a gain in visual acuity of 15 letters or more at the 12 month end point compared to observation. Conversely, the study also showed that over three quarters of the eyes that received IVT did not show a gain in vision by 15 letters or more at 12 months and a quarter of treated eyes had a loss of vision of a similar magnitude. The studies also demonstrated a 3–4 times greater rate of intraocular pressure elevation in the IVT (especially 4mg) arms compared to standard of care, and this together with a lack of definitive data to 2 years follow up beckons further studies on IVT and other agents, to search for improved outcomes and better side effect profiles.

Ozurdex (Allergan, Irvine, CA),[6] a biodegradable intravitreal 700 µg dexamethasone implant, received FDA approval in June 2009 for the treatment of macular edema secondary to BRVO or CRVO. Phase III results presented[55] showed that significantly more patients gained 15 letters or more in the treatment group compared to sham up to 90 days following injection, but this effect waned at 180 days to become nonsignificant. The effects of a repeat injection at 6 months were less pronounced when assessed at 12 months. Although designed to cause less intraocular pressure problems than

triamcinolone, 25% of those treated with Ozurdex showed an intraocular pressure rise which peaked at day 60 and returned to baseline by day 180. The incidence of cataract progression was noted at 4% in the treatment group, but this increased to 26% after 1 year where a second injection of Ozurdex had been carried out.

Anti-VEGF treatment

The anti-VEGF bevacizumab (Avastin, Genetech), a humanized monoclonal antibody binding to all isoforms of VEGF-A, was first reported to show short term efficacy in the resolution of macular edema secondary to CRVO by Rosenfeld in 2005[56] and has since been widely used as an off label treatment in RVO. Prager et al[57] have reported a prospective case series of patients with macular edema due to RVO and treated with bevacizumab, showing a mean increase in visual acuity of 16 letters at the 12-month follow up. Subgroup analysis showed a better response in patients with BRVO rather than CRVO, although the reduction in central retinal thickness (CRT) on optical coherence tomography was comparable in both subgroups. This incongruence between functional and anatomical effects was also reported in the SCORE-CRVO study,[52] where the observation and IVT groups had a comparable reduction in CRT at the 12 month point although visual outcomes were significantly better in the IVT groups.

Ranibizumab (Lucentis; Genentech, San Francisco, CA), approved for the treatment of neovascular age related macular degeneration (n-AMD), is a monoclonal antibody fragment derived from the same parent murine antibody as bevacizumab. The six-month data from two phase III Genentech-sponsored studies (BRAVO studying the effects of BRVO and CRUISE studying the effects of CRVO) evaluating the safety and efficacy of Lucentis, compared to sham, for the treatment of macular edema in RVO, were presented at the Retina Congress 2009.[58,59] BRAVO reported a 7.6 and 7.4 mean letter gain in the 0.3 mg and 0.5 mg study arms of Lucentis respectively, compared to 1.9 letters gained in the sham injection arm. CRUISE reported an 8.8 and 9.3 mean letter gain in the 0.3 mg and 0.5 mg study arms of Lucentis, respectively, compared with 1.1 letters gained in the sham treatment arm. Both studies showed a safety profile consistent with data from previous phase III Lucentis trials for n-AMD. Horizon RVO, an extension trial, will provide much needed longer term data upon completion of BRAVO and CRUISE.

Conclusion

Studies on n-AMD show that intravitreal treatment is accepted and well tolerated by patients. Corticosteroids and anti-VEGF medication currently seem to be at the forefront of treatment options for RVO, but RCTs have yet to compare these directly. Corticosteroids can be given as a depot with activity over several months, but the high incidence of intraocular pressure rise and cataract make them less attractive. Intravitreal anti-VEGFs have a low incidence of adverse side effects but are currently short acting requiring frequent injections. Both these agents are used as symptomatic treatments with no defined treatment end points and show high rates of regression and tachyphylaxis with loss of efficacy after repeated injections. There may also be a rebound phenomenon as observed by Matsumoto et al[60] with macular edema becoming more pronounced compared to pre-treatment levels.

Until a definitive treatment becomes available for RVO it is currently a case of using the various treatment options available to keep the macular dry (to prevent the irreversible damage caused by chronic macular edema) and titrating this to allow a sufficient collateral circulation to develop.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Cugati S, Wang JJ, Rochtchina E, et al. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2006;124:726–732.
2. Hayreh S. Prevalent misconceptions about acute retinal vascular occlusive disorders. *Prog Retinal Eye Res*. 2005;24:493–519.
3. Cheung N, Klein R, Wang J, et al. Traditional and novel cardiovascular risk factors for retinal vein occlusion: the multiethnic study of atherosclerosis. *Invest Ophthalmol Vis Sci*. 2008;49:4297–4302.
4. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. *Arch Ophthalmol*. 2008;126:513–518.
5. Dexamethasone 700 µg intravitreal implant in applicator for retinal vein occlusion. Allergan advance notification document. 2009 Oct.
6. Dexamethasone Intravitreal Implant Approved for Retinal Vein Occlusion. Medscape Medical News. Available from: http://www.medscape.com/viewarticle/704854. Accessed on March 1, 2010.
7. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117:313–319.
8. Green WR, Chan CC, Hutchins GM, et al. Central retinal vein occlusions: A prospective histopathologic study of 29 eyes in 28 cases. *Retina*. 1981;1:27–55.
9. The Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion. *Arch Ophthalmol*. 1996;114:545–554.
10. Sperduto RD, Hiller R, Chew E, et al. Risk factors for hemiretinal vein occlusion: comparison with risk factors for central and branch retinal vein occlusion: the eye disease case-control study. *Ophthalmology*. 1999;106:439–440.
11. The Eye Disease Case-Control Study Group. Risk factors for branch retinal vein occlusion. *Am J Ophthalmol*. 1993;116:286–296.
12. O'Mahoney P, Wong T, Ray J. Retinal vein occlusion and traditional risk factors for atherosclerosis. *Arch Ophthalmol*. 2008;126:692–699.
13. Koizumi H, Ferrara D, Brue C, et al. Central retinal vein occlusion case-control study. *Am J Ophthalmol*. 2007;144:858–863.

14. Fegan CD. Central retinal vein occlusion and thrombophilia. *Eye*. 2002;16:98–106.
15. Janssen MC, den Heijer M, Cruysberg JR, Wollersheim H, Bredie SJ. Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis? A meta-analysis of thrombophilic factors. *Thromb Haemost*. 2005;93:1021–1026.
16. Salaun N, Delyfer MN, Rougier MB, Korobelnik JF. Assessment of risk factors for retinal vein occlusions in patients under 60 years of age. *J Fr Ophtalmol*. 2007;30:918–923.
17. Turello M, Pasca S, Daminato R, et al. Retinal vein occlusion: evaluation of "classic" and "emerging" risk factors and treatment. *J Thromb Thrombolysis*. 2010;29:459–464.
18. Klein BE, Meuer SM, Knudtson MD, Klein R. The relationship of optic disk cupping to retinal vein occlusion: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;141:859–862.
19. Girmens JF, Scheer S, Heron E, et al. Familial central retinal vein occlusion. *Eye*. 2008;22:308–310.
20. Bhagat N, Goldberg MF, Gascon W, et al. Central retinal vein occlusion: report of two familial cases. *Eur J Ophthalmol*. 1999;9:181–195.
21. Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusion: implication of VEGF as a critical stimulator. *Mol Ther*. 2008;16:791–799.
22. Yoshimura T, Sonoda KH, Sugahara M, et al. Comprehensive analysis of inflammatory immune mediators in vitreoretinal diseases. *PLoS ONE* 2009;4(12):e8158.
23. Funk M, Kriechbaum K, Prager F, et al. Intraocular concentrations of growth factors and cytokines in retinal vein occlusion and the effect of therapy with bevacizumab. *Invest Ophthalmol Vis Sci*. 2009;50:1025–1032.
24. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331:1480–1487.
25. Ozaki H, Hayashi H, Vinores SA, Moromizato Y, Campochiaro PA, Oshima K. Intravitreal sustained release of VEGF causes retinal neovascularization in rabbits and breakdown of the blood-retinal barrier in rabbits and primates. *Exp Eye Res*. 1997;64:505–517.
26. Noma H, Funatsu H, Yamasaki M, et al. Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. *Am J Ophthalmol*. 2005;140:256–261.
27. Noma H, Funatsu H, Yamasaki M, et al. Aqueous humour levels of cytokines are correlated to vitreous levels and severity of macular edema in branch retinal vein occlusion. *Eye*. 2008;22:42–48.
28. Noma H, Funatsu H, Mimura T, Harino S, Sone T, Hori S. Increase of vascular endothelial growth factor and interleukin-6 in the aqueous humour of patients with macular edema and central retinal vein occlusion. *Acta Ophthalmol*. Epub 2009 Jun 26.
29. Noma H, Funatsu H, Mimura T, Harino S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor in macular edema with central retinal vein occlusion. *Ophthalmology*. 2009;116:87–93.
30. Boyd SR, Zachary I, Chakravarthy U, et al. Correlation of increased vascular endothelial growth factor with neovascularization and permeability in ischemic central vein occlusion. *Arch Ophthalmol*. 2002;120:1644–1650.
31. The Branch Vein Occlusion Study Group: Argon laser photocoagulation for macula edema in branch vein occlusion. *Am J Ophthalmol*. 1984;98:271–282.
32. The Branch Vein Occlusion Study Group: Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion. *Arch Ophthalmol*. 1986;104:34–41.
33. The Central Vein Occlusion Study Group: Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. *Ophthalmology*. 1995;102:1425–1433.
34. The Central Vein Occlusion Study Group: A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. *Ophthalmology*. 1995;102:1434–1444.
35. Rogers SL, McIntosh RL, Lim L, et al. Natural history of branch retinal vein occlusion: An evidence-based systematic review. *Ophthalmology*. 2010;117:1094–1101.e5.
36. Mohamed Q, McIntosh RL, Saw SM, Wong TY. Interventions for central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2007;114:507–519.
37. Squizzato A, Manfredi E, Bozzato S, et al. Antithrombotic and fibrinolytic drugs for retinal vein occlusion: A systematic review and a call for action. *Thromb Haemost*. 2010;103:271–276.
38. Lazo-Langner A, Hawel J, Ageno W, Kovacs MJ. Low molecular weight heparin for the treatment of retinal vein occlusion: a systematic review and meta-analysis of randomized trials. *Haematologica*. 2010; Mar 19 [Epub ahead of print].
39. Mandelcorn MS, Nrusimhadevara RK. Internal limiting membrane peeling for decompression of macular edema in retinal vein occlusion: a report of 14 cases. *Retina*. 2004;24:348–355.
40. Opremcak EM, Bruce RA, Lomeo MD, et al. Radial optic neurotomy for central retinal vein occlusion: a retrospective pilot study of 11 consecutive cases. *Retina*. 2001;21:408–415.
41. Weizer JS, Stinnett SS, Fekrat S. Radial optic neurotomy as treatment for central retinal vein occlusion. *Am J Ophthalmol*. 2003;136:814–819.
42. Weiss JN. Treatment of central retinal vein occlusion by injection of tissue plasminogen activator into a retinal vein. *Am J Ophthalmol*. 1998;126:142–144.
43. Bynoe LA, Hutchins RK, Lazarus HS, Friedberg MA. Retinal endovascular surgery for central retinal vein occlusion: initial experience of four surgeons. *Retina*. 2005;25:625–632.
44. McAllister IL, Gillies M, Smithies LA, et al. The central retinal vein bypass study: A trial of laser-induced chorioretinal venous anastomosis for central retinal vein occlusion. *Opthalmology*. 2010;117:954–965.
45. McIntosh RL, Mohamed Q, Saw SM, Wong TY. Interventions for branch retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2007;114:835–854.
46. Arnarsson A, Stefansson E. Laser treatment and the mechanism of edema reduction in branch retinal vein occlusion. *Invest Opthalmol Vis Sci*. 2000;41:877–879.
47. Muqit MM, Saidkasimova S, Keating D, Murdoch JR. Long-term study of vascular perfusion effects following arteriovenous sheathotomy for branch retinal vein occlusion. *Acta Ophthalmol*. 2010;88:e57–e65.
48. Park CH, Jaffe GJ, Fekrat S. Intravitreal triamcinolone acetonide in eyes with cystoid macular edema associated with central retinal vein occlusion. *Am J Ophthalmol*. 2003;136:419–425.
49. Ip MS, Gottlieb JL, Kahana A, et al. Intravitreal triamcinolone for the treatment of macular edema associated with central retinal vein occlusion. *Arch Ophthalmol*. 2004;122:1131–1136.
50. Patel PJ, Zaheer I, Karia N. Intravitreal triamcinolone acetonide for macular edema owing to retinal vein occlusion. *Eye*. 2008;22:60–64.
51. Miyamoto N, Iossifov D, Metge F, Behar-Cohen F. Early effects of intravitreal triamcinolone on macular edema. *Ophthalmology*. 2006;113:2048–2053.
52. The SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the standard care vs corticosteroid for retinal vein occlusion (SCORE) Study Report 5. *Arch Ophthalmol*. 2009;127:1101–1114.
53. The SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the standard care vs corticosteroid for retinal vein occlusion (SCORE) Study Report 6. *Arch Ophthalmol*. 2009;127:1115–1128.
54. Apte RS. SCOREing in retinal venous occlusive disease. *Arch Ophthalmol*. 2009;127:1203–1204.
55. Loewenstein A, Haller J, Bandello F, et al. 12-month evaluation of an applicator-delivered dexamethasone intravitreal implant in patients with macular edema due to branch or central retinal vein occlusion. Paper presented at: the 33rd Annual Macula Society Meeting; 2010 Feb 26; Tuscon, AZ.

56. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for macular edema from central vein occlusion. *Ophthalmic Surg Lasers Imaging*. 2005;36:336–339.
57. Prager F, Michels S, Kriechbaum K, et al. Intravitreal bevacizumab (Avastin) for macular edema secondary to retinal vein occlusion: 12-month results of a prospective clinical trial. *Br J Ophthalmol*. 2009; 93:452–456.
58. Campochiaro PA. Safety and efficacy of intravitreal ranibizumab (Lucentis) in patients with macular edema secondary to branch retinal vein occlusion: The BRAVO Study. Paper presented at: Retina Congress 2009; Oct 4; New York.
59. Brown DM. Safety and efficacy of intravitreal ranibizumab (Lucentis) in patients with macular edema secondary to central retinal vein occlusion: The CRUISE Study. Paper presented at: Retina Congress 2009 Oct 4; New York.
60. Matsumoto Y, Freund KB, Peiretti E, Cooney MJ, Ferrara DC, Yannuzzi LA. Rebound macular edema following bevacizumab (Avastin) therapy for retinal venous occlusive disease. *Retina*. 2007; 27:426–431.

The RESTORE Study

Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema

*Paul Mitchell, MD, PhD,[1] Francesco Bandello, MD, FEBO,[2] Ursula Schmidt-Erfurth, MD,[3] Gabriele E. Lang, MD,[4] Pascale Massin, MD, PhD,[5] Reinier O. Schlingemann, MD, PhD,[6] Florian Sutter, MD,[7] Christian Simader, MD,[8] Gabriela Burian, MD, MPH,[9] Ortrud Gerstner, MSc,[9] Andreas Weichselberger, PhD,[9] on behalf of the RESTORE study group**

Objective: To demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone based on mean average change in best-corrected visual acuity (BCVA) over 12 months in diabetic macular edema (DME).

Design: A 12-month, randomized, double-masked, multicenter, laser-controlled phase III study.

Participants: We included 345 patients aged ≥18 years, with type 1 or 2 diabetes mellitus and visual impairment due to DME.

Methods: Patients were randomized to ranibizumab + sham laser (n = 116), ranibizumab + laser (n = 118), or sham injections + laser (n = 111). Ranibizumab/sham was given for 3 months then pro re nata (PRN); laser/sham laser was given at baseline then PRN (patients had scheduled monthly visits).

Main Outcome Measures: Mean average change in BCVA from baseline to month 1 through 12 and safety.

Results: Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 vs +0.8; both $P<0.0001$). At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and BCVA letter score level >73 (20/40 Snellen equivalent) with ranibizumab (22.6% and 53%, respectively) and ranibizumab + laser (22.9% and 44.9%) versus laser (8.2% and 23.6%). The mean central retinal thickness was significantly reduced from baseline with ranibizumab (−118.7 μm) and ranibizumab + laser (−128.3 μm) versus laser (−61.3 μm; both $P<0.001$). Health-related quality of life, assessed through National Eye Institute Visual Function Questionnaire (NEI VFQ-25), improved significantly from baseline with ranibizumab alone and combined with laser ($P<0.05$ for composite score and vision-related subscales) versus laser. Patients received ~7 (mean) ranibizumab/sham injections over 12 months. No endophthalmitis cases occurred. Increased intraocular pressure was reported for 1 patient each in the ranibizumab arms. Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study.

Conclusions: Ranibizumab monotherapy and combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to DME. Visual acuity gains were associated with significant gains in VFQ-25 scores. At 1 year, no differences were detected between the ranibizumab and ranibizumab + laser arms. Ranibizumab monotherapy and combined with laser had a safety profile in DME similar to that in age-related macular degeneration.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Ophthalmology 2011;118:615–625

**Group members listed online in Appendix (available at http:///aaojournal.org)*

Diabetic macular edema (DME) is a leading cause of visual impairment in patients with diabetic retinopathy.[1–3] Focal/grid laser photocoagulation (hereafter referred to as laser), the current standard of care in DME, is mostly associated with only vision stabilization. Some recent trials, however, have demonstrated useful vision gain with laser; for example, the Diabetic Retinopathy Clinical Research Network (DRCR.net) study group recently reported a 10-letter gain in 31% patients, whereas 19% of laser-treated patients exhibited progressive visual loss (worsening by ≥2 lines after 2 years follow-up), at a risk of developing scotomas.[4–7]

Vascular endothelial growth factor (VEGF) levels are elevated in the vitreous of eyes with diabetic retinopathy making anti-VEGF treatment an attractive therapeutic modality in DME.[8] Recently, the DRCR.net study group reported that ranibizumab 0.5 mg combined with either prompt or deferred laser therapy was significantly more effective than laser alone in improving vision in patients with DME after 1 year of treatment (best-corrected visual

ISSN 0161-6420/11
doi:10.1016/j.ophtha.2011.01.031

acuity [BCVA] letter score of +9 for both ranibizumab groups vs +3 for laser; $P<0.001$).[9] The RESOLVE study (phase II randomized multicenter) demonstrated that ranibizumab monotherapy was well-tolerated and significantly more effective than sham treatment (with rescue laser) in providing rapid and continuous improvements in BCVA over 12 months (mean BCVA letter score change from baseline to month 12, +10.3 for ranibizumab vs −1.4 for sham; $P<0.0001$).[10]

Apart from Ranibizumab for Edema of the mAcula in Diabetes study (READ-2),[11] there have been no other randomized controlled trials that have assessed the efficacy and safety of ranibizumab monotherapy compared with laser monotherapy. Additionally, it is not yet established whether ranibizumab monotherapy is superior or at least equivalent to combined therapy. The 12-month, phase III, randomized, double-masked, multicenter, laser-controlled RESTORE study was designed to assess whether ranibizumab monotherapy or combined with laser was superior to laser alone in patients with visual impairment due to DME. In addition, RESTORE is the first study to assess the impact of ranibizumab treatment on health-related quality of life (HRQoL) outcomes in patients with DME.

Materials and Methods

Study Design

The RESTORE study was a 12-month, double-masked, multicenter, laser-controlled, phase III study where 345 eligible patients from 73 centers (10 European countries, Turkey, Canada, and Australia) were randomized 1:1:1 to 1 of the 3 treatment arms: Intravitreal ranibizumab (0.5 mg) injection + sham laser, adjunctive administration of intravitreal ranibizumab (0.5 mg) injection + active laser, or laser treatment + sham injections for 12 months (for details of randomization and masking, see Appendix 1, available online at http://aaojournal.org). One eye was selected and treated as the study eye. If both eyes were eligible, the eye with the worse visual acuity (VA; assessed at visit 1) was selected for treatment, unless, based on medical reasons, the investigator deemed the other eye more appropriate to receive study treatment. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Approval was obtained from the ethics committee or institutional review board at each contributing center. Patients provided written informed consent before entering the study. The study is registered with clinicaltrials.gov as NCT00687804.

Patients. The study population consisted of 345 male and female patients ≥18 years of age with either type 1 or 2 diabetes mellitus (as per American Diabetes Association or World Health Organization guidelines), glycosylated hemoglobin (HbA1c) ≤10%, and visual impairment due to DME. The key inclusion criteria were (1) stable medication for the management of diabetes within 3 months before randomization and expected to remain stable during the study; (2) visual impairment due to focal or diffuse DME (definition in Table 1) in at least 1 eye that was eligible for laser treatment in the opinion of the investigator; (3) BCVA letter score between 78 and 39, both inclusive, based on Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA testing charts administered at a starting distance of 4 meters (approximate Snellen equivalent 20/32–20/160); and (4) decreased vision due to DME and not other causes, in the investigator's opinion (at visit 1). The key exclusion criteria were (1) concomitant conditions in the study eye that could prevent the improvement in VA on the study treatment in the investigator's opinion; (2) active intraocular inflammation or infection in either eye; (3) uncontrolled glaucoma in either eye (e.g., intraocular pressure [IOP] > 24 mmHg on medication, or from the investigator's

Table 1. Key Baseline Demographic and Disease Characteristics (Randomized Set)

Variable	Ranibizumab 0.5 mg (n = 116)	Ranibizumab 0.5 mg + Laser (n = 118)	Laser (n = 111)
Mean age ± SD (years)	62.9±9.29	64.0±8.15	63.5±8.81
Gender, n (%)			
Men	73 (62.9)	70 (59.3)	58 (52.3)
Women	43 (37.1)	48 (40.7)	53 (47.7)
Diabetes type, n (%)			
Type I	13 (11.2)	15 (12.7)	13 (11.7)
Type II	103 (88.8)	102 (86.4)	97 (87.4)
Not stated	0	1 (0.8)	1 (0.9)
Mean time since first diagnosis of diabetes ± SD (years)	15.23±9.91	14.62±9.84	12.93±9.02
Mean time since first diagnosis of DME ± SD (years)	1.80±1.98	1.99±3.14	1.58±1.96
DME type, n (%)*			
Focal	64 (55.2)	68 (57.6)	53 (47.7)
Diffuse	45 (38.8)	46 (39.0)	52 (46.8)
Missing	7 (6.0)	4 (3.4)	6 (5.4)
Mean VA ± SD (letter score)	64.8±10.11	63.4±9.99	62.4±11.11
Patients with VA letter score >73, n (%)	23 (19.8)	19 (16.1)	17 (15.3)
Mean CRT ± SD (μm)	426.6±118.01	416.4±119.91	412.4±123.95

CRT = central retinal thickness; DME = diabetic macular edema; SD = standard deviation; VA = visual acuity.
*Focal DME: More than 67% of leakage originated from leaking microaneurysms (MAs) in the whole edema area or 30%–67% leakage from MAs in the whole edema area, but >67% of the leakage originated from MAs in the central subfield.
Diffuse DME: Less than 33% of leakage originated from leaking MAs the rest from diffuse leaking capillaries in the whole edema area or 30%–67% leakage comes from MAs, but <33% of the leakage originated from MAs in the central subfield.

judgment); (4) panretinal laser photocoagulation (within 6 months) or focal/grid laser photocoagulation (within 3 months) before study entry; (5) treatment with antiangiogenic drugs in the study eye within 3 months before randomization; (6) history of stroke; and (7) systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg, untreated hypertension, or change in antihypertensive treatment within 3 months preceding baseline.

Study Objectives. The primary objective of this study was to demonstrate superiority of ranibizumab 0.5 mg as monotherapy or combined with laser therapy over laser alone (the current standard of care) with respect to mean average change in BCVA from baseline over 12 months. Secondary objectives were to evaluate (1) if ranibizumab 0.5 mg as monotherapy or adjunctive to laser was superior to laser alone in the proportion of patients with VA improvement and with BCVA letter score >73 (20/40 Snellen equivalent) at month 12; (2) the time course of mean change in BCVA letter score and central retinal (subfield) thickness (CRT); (3) patient-reported outcomes relative to those associated with laser treatment; and (4) the safety of intravitreal injections of ranibizumab 0.5 mg, as monotherapy or adjunctive to laser therapy relative to laser treatment.

Efficacy and Safety Assessments

Best-Corrected Visual Acuity. We assessed BCVA at every study visit using ETDRS charts at a starting distance of 4 meters. The primary efficacy end point was the mean average change in BCVA letter score from baseline to month 1 through month 12. Secondary efficacy end points included the mean BCVA letter score change from baseline to month 12 and proportion of patients who gained ≥10 and ≥15 letters in BCVA and patients with BCVA letter score >73 at month 12. Mean average change in BCVA from baseline to month 1 through month 12 was chosen as the primary efficacy end point as it accounts for both interpatient and intramonth variability in BCVA and thus gives a more robust estimate of the VA gained by patients over time compared with the mean change of BCVA from baseline to study end.

A subgroup analysis of the primary end point was performed on the basis of demographic and baseline disease characteristics. The key categories assessed were as follows: DME type (focal/diffuse), BCVA letter score (≤60, 61–73, and >73), diabetes type (type 1/type 2), focal and/or grid laser pretreatment (yes/no), CRT (<300, 300–400, and >400 μm), ETDRS retinopathy severity score (10–35, 43 or 47, and 53–85), macular ischemia (yes/no; measured by the presence of capillary loss on fluorescein angiography according to a modified ETDRS grading scale in the center subfield of 1000 μm diameter, where the capillary loss grades "moderate," "severe," or "completely destroyed" were categorized as "yes" ischemia, and the grades "none" or "mild" were classified as "no" ischemia).

Optical Coherence Tomography. Optical coherence tomography (OCT) was performed at every study visit using Stratus OCT (Carl Zeiss, Meditec, Dublin, CA). The images were reviewed by a central reading center to ensure a standardized evaluation. Retinal thickness was determined using individual A-scans along with each of 6 B-scans. End points included mean change in CRT (defined from the central macular area 1000 μm in diameter) over time and the proportion of patients with CRT <275 μm.

Stereoscopic Color Fundus Photography and Fluorescein Angiography. Stereoscopic color fundus photography and fluorescein angiography were performed at baseline, month 6, and month 12. After pupil dilation and before fluorescein dye injection, red-free and ETDRS 7-field color photographic images of the retina of the study eye were taken. Anatomic end points included the proportion of patients with resolution of leakage and cysts at month 12 as assessed by the central reading center and the proportion of patients with a 3-step change in the ETDRS severity score from baseline to month 12 (exploratory end point).

Health-Related Quality of Life. We assessed HRQoL using the visual-specific National Eye Institute Visual Function Questionnaire (NEI VFQ-25), as well as generic health assessment utility tools EuroQoL (EQ-5D), and time trade off (TTO). All questionnaires were scored by patients at baseline and month 12. Additionally, the NEI VFQ-25 was scored at month 3 and the EQ-5D was scored at months 3 and 6. End points included the absolute change in scores, changes in scores over time, and differences in scores between treatment groups.

Drug Exposure. The number of ranibizumab/sham injections and active/sham laser treatments, and the mean duration of treatment-free intervals (ranibizumab/sham injection, active/sham laser) were evaluated over the 12-month assessment period for each of the treatment arms.

Safety Assessments. Safety was assessed by the 12-month incidence of adverse events (AEs) and serious AEs (SAEs), by ophthalmic examinations and IOP measurements, and by changes in vital signs and laboratory parameters over the 12-month assessment period.

Treatment

Ranibizumab/Sham Treatment. Patients received 3 initial consecutive monthly injections of ranibizumab (months 0–2; treatment initiation phase), followed by further treatment according to protocol-defined retreatment criteria between and including months 3 and 11 (continuous/resumed treatment phase; Figure 1, available online at http://aaojournal.org). Intravitreal ranibizumab injections were performed by the investigators' usual routines; both pre- and postinjection topical antibiotics were used. Sham ranibizumab injection involved imitation of an injection procedure using an injection syringe without needle, by applying pressure against the globe.

Retreatment Criteria During Continuous/Resumed Treatment Phase. As of month 3, the protocol required that 1 injection per month was to be continued if stable VA was not reached. Treatment was suspended if either of the following criteria were met: (1) if the investigator's opinion was that no (further) BCVA improvement was attributable to treatment with intravitreal injection at the last 2 consecutive visits, or (2) BCVA letter score ≥ 84 (approximate Snellen equivalent 20/20) was observed at the last 2 consecutive visits. After suspension, injections were resumed pro re nata (PRN [as required]) if there was a decrease in BCVA due to DME progression, confirmed by clinical evaluation and/or OCT or other anatomic and clinical assessments, in the opinion of the investigator. Patients were treated at monthly intervals until stable VA was reached again. Thus, reinitiation of intravitreal injections encompassed ≥2 successive monthly treatments.

Laser/Sham Laser Treatment. The first laser treatment (active or sham depending on treatment group; the ranibizumab + sham laser group did not receive active laser treatment) was administered on day 1. If required, the first laser administration could be split into 2 sessions, 4 weeks apart. Retreatments were given in accordance with ETDRS guidelines at intervals no shorter than 3 months from the previous treatment if deemed necessary by the evaluating investigator. Patients receiving retreatment with active or sham laser continued to be treated with monthly ranibizumab or sham injections as long as the treatment criteria for intravitreal injection were fulfilled. Decisions on retreatment with laser/sham were independent of decisions to administer ranibizumab/sham injections and vice versa. Sham laser was applied under the same procedure used for laser treatment but without switching on the laser beam, and by imitating depression of the laser pedal.

Statistical Analysis

The primary analysis was performed on the full analysis set (FAS), consisting of all patients who received ≥1 application of the study treatment ([sham] injection and/or [sham] laser) and had ≥1 postbaseline assessment for BCVA. The primary end point was the difference between the average BCVA letter score over all monthly postbaseline assessments from month 1 to month 12 and the baseline BCVA letter score (= average change from baseline).

The analysis of the primary end point used the last observation carried forward approach for the imputation of missing data. Sensitivity analyses of the primary end point were performed using (1) an "as documented" approach in the FAS where the average change from baseline in BCVA was calculated from observed changes only, and (2) a per-protocol set with missing data being handled in the same way as for the FAS.

A sample size of 105 randomized patients per treatment group was considered to have >90% power to detect a 5-letter BCVA score treatment difference in the mean average change in BCVA compared with baseline from month 1 through month 12, assuming a standard deviation (SD) of 10 BCVA letter score with a Bonferroni adjusted 1-sided alpha level of 0.0125 for the 2 comparisons. Hypothesis testing of the superiority of ranibizumab mono and/or ranibizumab/laser combination compared with laser was done in parallel according to the Hochberg procedure controlling the overall 1-sided alpha level at 0.025. The statistical hypothesis testing of the average change from baseline in BCVA was based on the stratified Cochran–Mantel–Haenszel test using the observed values as scores and with stratifications according to DME type (focal, diffuse) and baseline BCVA letter score (≤60, 61–73, >73). Two-sided 95% confidence intervals for the mean average changes in BCVA and for the corresponding pair-wise difference between treatments, were calculated using the least-square means from an analysis of variance model with treatment, DME type, and baseline BCVA category (see above) as factors.

The safety analysis was conducted on the safety set that comprised all patients who received ≥1 application of study treatment and had ≥1 postbaseline safety assessment.

Results

Patient Disposition and Demographics

A total of 345 patients were randomized to receive ranibizumab 0.5 mg (n = 116), ranibizumab 0.5 mg + laser (n = 118), or laser (n = 111). The efficacy analysis was performed on the FAS that comprised 115 (ranibizumab 0.5 mg), 118 (ranibizumab + laser), and 110 (laser) patients (1 patient each from the ranibizumab and laser arm were excluded because they had no postbaseline VA data). The safety analysis was conducted on the safety set comprising 115 (ranibizumab), 120 (ranibizumab + laser), and 110 (laser) patients. Three patients (1 in each treatment arm) received active ranibizumab and active laser in the study eye at baseline without consideration of the randomization, and all 3 of these were analyzed under the ranibizumab + laser arm for the safety set. The patient disposition was comparable across the 3 treatment groups (Fig 2, available online at http://aaojournal.org); 87.9% (ranibizumab), 87.3% (ranibizumab + laser), and 88.3% (laser) of the patients completed the 12-month study period. There were 2 deaths in each of the 3 treatment arms. Baseline demographics and diabetes characteristics were comparable across the 3 treatment arms (Table 1).

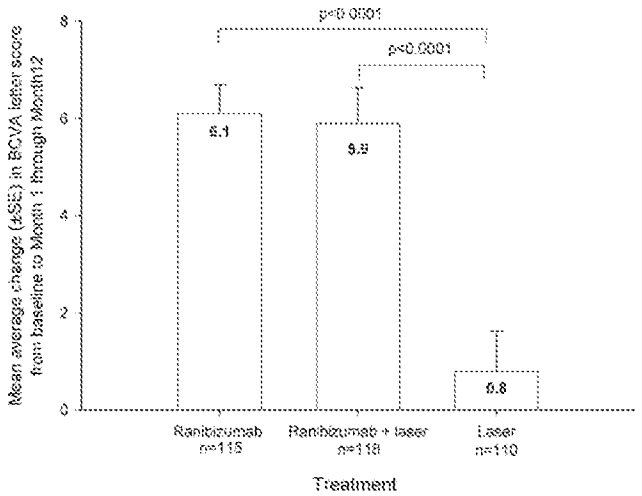


Figure 3. Mean average change in best-corrected visual acuity (BCVA) letter score from baseline to months 1 through 12 (primary end point). SE = standard error.

Efficacy

Best-Corrected Visual Acuity. The mean average change ± SD in the BCVA letter score from baseline to month 1 through month 12 was significantly superior with ranibizumab (6.1 ± 6.4; $P<0.0001$) and ranibizumab + laser (5.9 ± 7.9; $P<0.0001$) than with laser treatment (0.8 ± 8.6), hence the primary end point was achieved (Fig 3; Table 2). There was no difference detected between the 2 ranibizumab treatment arms ($P = 0.61$, Cochran–Mantel–Haenszel test). Similar results were obtained (data not shown) for the primary end point using the "as documented" approach and the per protocol set. The last observation carried forward calculation of the average level of BCVA letter score over all monthly post-baseline assessments from month 1 to month 12 was based on 92.6% (ranibizumab), 92.9% (ranibizumab + laser), and 91.4% (laser) observed monthly BCVA assessments.

The mean change ± SD in BCVA letter score from baseline to month 12 was 6.8 ± 8.3 ($P<0.0001$) in the ranibizumab arm, 6.4 ± 11.8 ($P = 0.0004$) in the ranibizumab + laser arm, and 0.9 ± 11.4 in the laser arm (Table 2). In the ranibizumab and ranibizumab + laser arms, a rapid and clinically relevant improvement in mean BCVA was observed as of the first assessment posttreatment (at month 1), which continued up to month 3 and was sustained at the month 3 level until the last assessment time point at month 12. In the laser arm, mean BCVA stabilized around baseline level and reached a 0.9 letter gain at month 12 (Fig 4A).

At month 12, 53.0% (vs 19.8% at baseline) of patients in the ranibizumab arm and 44.9% (vs 16.1% at baseline) of patients in the ranibizumab + laser arm had a BCVA letter score >73 (20/40 Snellen equivalent) compared with 23.6% (vs 15.3% at baseline) of patients in the laser arm (estimated treatment difference vs laser, 29.4% [95% confidence interval, 17.3–41.5] for ranibizumab and 21.3% [95% confidence interval, 9.3–33.3] for ranibizumab + laser; Table 2; month 3 and 6 data in Table 3, available online at http://aaojournal.org).

A significantly greater proportion of patients gained ≥5 BCVA letters with ranibizumab (65.2% [ranibizumab] and 63.6% [ranibizumab + laser]; $P<0.0001$) versus laser alone (33.6%). Similarly, a significantly greater proportion of patients in either the ranibizumab arm or the ranibizumab + laser arm compared with the laser arm gained a ≥10 BCVA letter score (37.4% and 43.2% vs 15.5%; $P<0.0001$ for both) and a ≥15 BCVA letter score (22.6% [$P = 0.0005$] and 22.9% [$P = 0.0037$] vs 8.2%; Table 2). Con-

Table 2. Best-Corrected Visual Acuity (BCVA) and Central Retinal Thickness (CRT) Outcome at Month 12 (Full Analysis Set, Last Observation Carried Forward)

	Ranibizumab 0.5 mg (n = 115)	Ranibizumab 0.5 mg + Laser (n = 118)	Laser (n = 110)
Mean average change in BCVA letter score from baseline to month 1–12 (primary end point)*			
Mean ± SD	6.1±6.43	5.9±7.92	0.8±8.56
Median (range)	6.1 (−10.9–25.2)	6.0 (−26.7–27.6)	1.3 (−37.8–26.8)
95% CI for mean**	(4.9, 7.3)	(4.4, 7.3)	(−0.8, 2.4)
Comparison verus laser			
Difference in LS means (vs laser)†	5.4	4.9	
95% CI for difference†	(3.5, 7.4)	(2.8, 7.0)	
P value‡	<0.0001	<0.0001	
Proportion of patients with BCVA letter score >73 at month 12			
n (%)	61 (53.0)	53 (44.9)	26 (23.6)
95% CI for percentage	(43.5, 62.4)	(35.7, 54.3)	(16.1, 32.7)
Difference in percentage (vs laser)	29.4	21.3	
95% CI for difference	(17.3, 41.5)	(9.3, 33.3)	
P value‡	<0.0001	0.0002	
Categorized BCVA letter score outcome at month 12, n (%)			
Gain of ≥5	75 (65.2)	75 (63.6)	37 (33.6)
Gain of ≥10§	43 (37.4)	51 (43.2)	17 (15.5)
Loss of ≥10	4 (3.5)	5 (4.2)	14 (12.7)
Gain of ≥15§	26 (22.6)	27 (22.9)	9 (8.2)
Loss of ≥15	1 (0.9)	4 (3.4)	9 (8.2)
Mean CRT change from baseline to month 12, μm			
Mean ± SD	−118.7±115.07	−128.3±114.34	−61.3±132.29
Median (range)	−103.0 (−514–120)	−116.5 (−487–103)	−60.0 (−451–329)
95% CI for mean**	(−140.1, −97.3)	(−149.3, −107.3)	(−86.5, −36.1)
Comparison verus laser			
Difference in LS means (vs laser)†	−61.5	−70.6	
95% CI for difference†	(−93.8, −29.2)	(−102.1, −39.0)	
P value‡	0.0002	<0.0001	

ANOVA = analysis of variance; CI = confidence intervals; LS = least square; SD = standard deviation.
*Missing VA values imputed using last observation carried forward for 7.39% (ranibizumab), 7.06% (ranibizumab + laser) and 8.56% (laser) patients.
**Two-sided 95% CI are based on the t-distribution.
†Differences in LS means and the 2-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
‡*P*-values for treatment difference are from the 2-sided stratified Cochran-Mantel-Haenszel test using the row means score.
§Specified gain, or BCVA letter score of ≥84.

versely, a lower proportion of patients lost ≥10 and ≥15 letters in both the ranibizumab arms compared with the laser arm.

The mean average BCVA change from baseline to month 1 through month 12 by some of the key subgroups including patients with/without macular ischemia and those with focal/diffuse DME are presented in Figure 5A–E (Fig 5C–E and Fig 6 [mean average change in BCVA], available online at http://aaojournal.org). Each of the ranibizumab patient subgroups did better on average than those on laser alone in terms of the primary efficacy end point (all categories presented in Table 4 available online at http://aaojournal.org).

Central Retinal Thickness. The mean CRT change from baseline to month 12 decreased significantly for ranibizumab (118.7 μm; $P = 0.0002$) and ranibizumab + laser (128.3 μm; $P<0.0001$) compared with laser (61.3 μm; Fig 4B; Table 2).

At month 12, the proportion of patients with CRT < 275 μm was significantly greater in the ranibizumab monotherapy arm (49.1%; $P = 0.0408$) and the ranibizumab + laser arm (55.1%; $P = 0.0075$) compared with the laser arm (39.1%).

Colour Fundus Photography and Fluorescein Angiography

At month 12, a significantly larger proportion of patients had resolution of leakage in the ranibizumab (19.4%; $P = 0.0002$) and the ranibizumab + laser (13.7%; $P = 0.0114$) arms compared with the laser arm (2.2%).

Health-Related Quality of Life

Visual Functioning Questionnaire. The mean changes in the NEI VFQ-25 composite scores by treatment arms at months 3 and 12 are presented in Figure 7A (available at online http://aaojournal.org). For both ranibizumab arms the composite scores increased from month 3 to 12, whereas it decreased for the laser arm. At month 12, there was a greater improvement in the composite scores in the ranibizumab (5.0; $P = 0.014$) and ranibizumab + laser (5.4; $P = 0.004$) arms compared with the laser arm. At month 12, greater differences from baseline in NEI VFQ-25 subscale scores (general vision, near activities, and distance activities) were observed for ranibizumab and ranibizumab + laser versus laser alone (all $P<0.05$; Fig 7B–D).

At month 12, excellent to good eyesight was reported by 46% and 50% of the patients in the ranibizumab and ranibizumab + laser arm compared with 21% and 23% of the patients at baseline (determined by the individual NEI VFQ-25 question pertaining to patient's perception of eyesight posttreatment). Excellent to good vision was reported by only 24% patients with laser alone at month 12 compared with 22% of the patients at baseline.

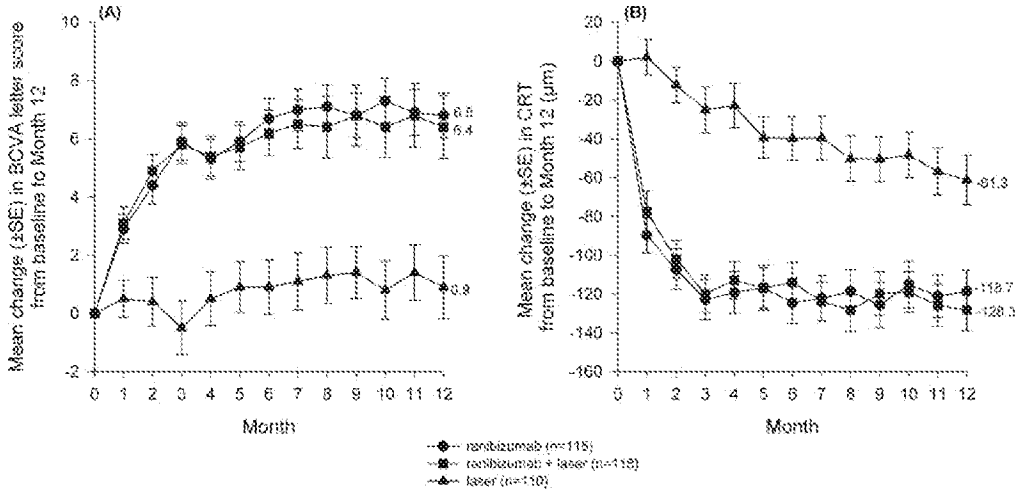


Figure 4. A, Mean change in best-corrected visual acuity (BCVA) letter score from baseline to month 12. B, Mean change in central retinal thickness (CRT) from baseline to month 12. SE = standard error.

EQ-5D Scores. None of the differences from baseline in the mean EQ-5D visual analog scores between the ranibizumab treatment groups and laser alone were statistically significant at any time point (Fig 8, available online at http://aaojournal.org).

TTO Scores. Patients were asked what proportion of their life expectancy they would be willing to trade off to avoid their current vision impaired health state, the resulting proportion representing the utility of their current health state. An improvement of 0.13 in the utility score was observed for ranibizumab monotherapy (baseline score 0.69), 0.032 for ranibizumab + laser (baseline score 0.73), and 0.023 for laser alone (baseline score 0.73; Fig 9, available online at http://aaojournal.org); these differences were not significant versus laser.

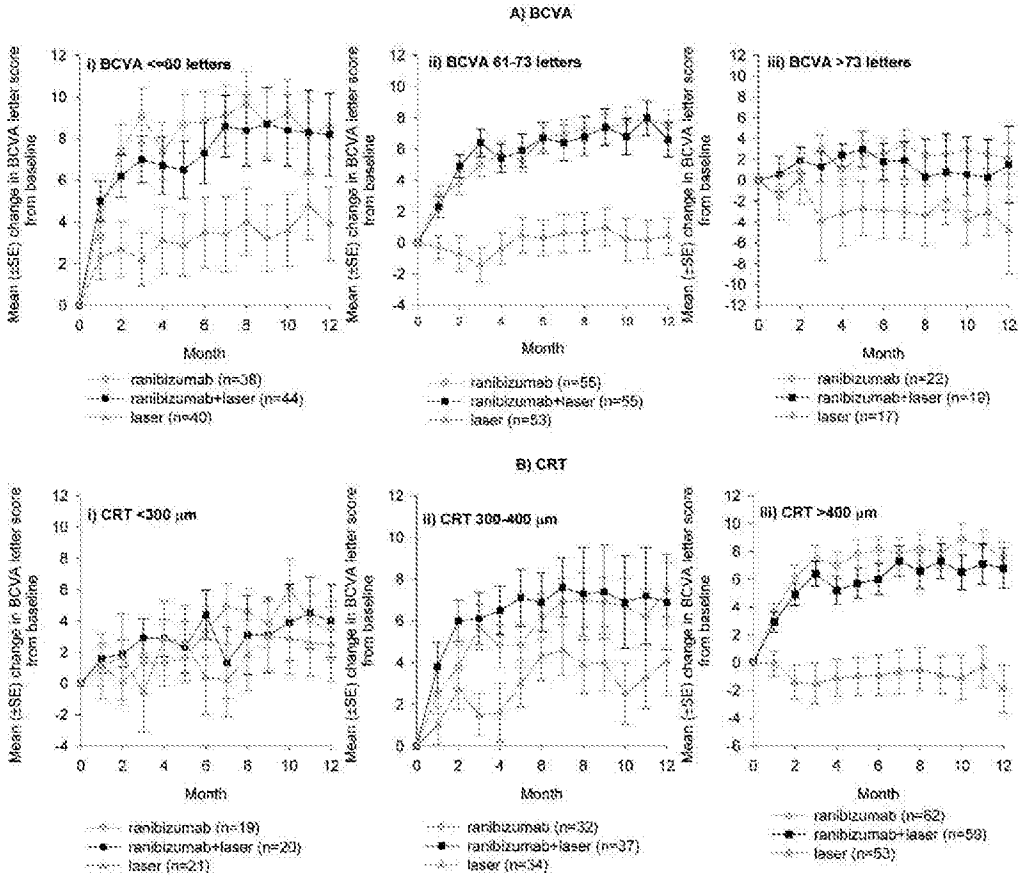


Figure 5. Mean change in best-corrected visual acuity (BCVA) from baseline over 12 months by key baseline characteristics, (A) best-corrected visual acuity and (B) central retinal thickness. BCVA = best-corrected visual acuity; CRT = central retinal thickness; SE = standard error.

Table 5. Number of Ranibizumab/Sham Injections Received (Safety Set)

	Ranibizumab 0.5 mg (n = 115)	Ranibizumab 0.5 mg + Laser (n = 120)	Laser (n = 110)
Total number of injections	Ranibizumab	Ranibizumab	Sham
Total	800	816	802
Mean ± SD	7.0±2.81	6.8±2.95	7.3±3.22
Median (Range)	7.0 (1–12)	7.0 (2–12)	7.0 (1–12)
Distribution of injections, n (%)			
1–3	16 (13.9)	23 (19.2)	19 (17.3)
4–6	37 (32.2)	34 (28.3)	32 (29.1)
7–9	40 (34.8)	35 (29.2)	22 (20.0)
10–12	22 (19.1)	28 (23.3)	37 (33.6)

SD = standard deviation.

Drug Exposure

Ranibizumab Injections. The mean number of ranibizumab/sham injections received was similar for all treatment groups (6.8–7.3 injections; Table 5). Between months 3 and 11, patients received an average of 4.1 ranibizumab intravitreal injections in the ranibizumab arm, 3.8 in the ranibizumab + laser arm, and 4.5 sham injections in the laser-treated arm.

Treatment-Free Interval for Ranibizumab or Sham Injections. A greater proportion of patients in the ranibizumab (85.2%) and ranibizumab + laser arms (81.7%) had their dose interrupted due to disease improvement compared with the laser arm (68.2%), which received sham injections only (Table 6 available online at http://aaojournal.org). According to the protocol, the first possible time point to stop injections (ranibizumab or sham) because of stability was month 3. At month 3, more patients in the ranibizumab arms (32.2% [ranibizumab] and 30.8% [ranibizumab + laser]) than the laser arm (20.9%) were not treated because of stability of VA.

After treatment interruption, the mean duration of the treatment-free interval was approximately 2 months in both the ranibizumab and the laser arms and approximately 2.5 months in the ranibizumab + laser arm (Table 7 available online at http://aaojournal.org). Fewer patients received monthly treatment in the ranibizumab (8.0%) and ranibizumab + laser (7.6%) arms compared with the laser arm (17.8%). The proportion of patients with a maximum treatment-free interval of ≥3 months was similar across treatment arms (57.9%–61.9%).

Laser Treatment. The mean number of active/sham laser treatments was similar for all treatment groups (1.7–2.1 administrations; Table 8 available online at http://aaojournal.org). From month 3 to month 11, patients received 0.9 sham laser administrations in the ranibizumab arm, 0.7 active laser administrations in the ranibizumab + laser arm, and 1.1 in the laser-treated arm (Table 8, available online at http://aaojournal.org). During this period, 49.6% (ranibizumab) and 44.5% (ranibizumab + laser) of the patients received a sham/active laser treatment compared with 63.9% patients in the laser arm.

Safety

Serious Adverse Events. No ocular SAEs were reported in the ranibizumab arm, whereas there were 2 cases each reported in the ranibizumab + laser (cataract) and laser only (cataract and maculopathy) arms; none suspected to be related to study drug or procedure (Table 9 available online at http://aaojournal.org). There were no cases of endophthalmitis reported in any of the treatment arms (~7 ranibizumab or sham injections over the 12-month treatment period). There were 23 (20%) patients with nonocular SAEs in the ranibizumab arm, 17 (14.2%) in the ranibizumab + laser arm, and 15 (13.6%) in the laser arm (Table 9, available online at http://aaojournal.org). The nonocular SAEs that were suspected by the investigator to be related to a study drug or procedure included intestinal obstruction (0.9%), hypoglycemia (0.9%), pulmonary embolism (1.7%), dyspnea (0.9%), and arterial thrombosis limb (0.9%) in the ranibizumab arm, coronary artery occlusion (0.8%) in the ranibizumab + laser arm. There were 6 deaths reported during the study (2 per treatment arm), none of which were considered to be related to the study drug by the investigator (Table 9, available online at http://aaojournal.org).

Adverse Events. The most frequently occurring ocular and nonocular AEs are summarized in Table 10 (available online at http://aaojournal.org). The most common ocular AE was eye pain in all 3 treatment arms. Eye pain was also the most common ocular AE suspected to be related to study drug (10–12 cases) followed by conjunctival hemorrhage, which was reported in the ranibizumab arms only (8–9 cases). One patient each in the ranibizumab arms experienced IOP increase, which was suspected to be related to study drug or procedure (Table 11 available online at http://aaojournal.org). Nasopharyngitis was the most common nonocular AE observed in all 3 treatment arms. Some of the nonocular AEs that were suspected to be related to study drug or procedure included pulmonary embolism (n = 2), limb arterial thrombosis (n = 1), arthralgia (n = 1), and hypertension (n = 1), all in the ranibizumab arm, coronary artery occlusion (n = 1) in the ranibizumab + laser arm, and hypertension (n = 1) in the sham arm (Table 11). Hypertension, the most common AE potentially related to systemic VEGF inhibition, was comparable in all treatment arms (Table 12). Arterial thromboembolic events were reported by 6 patients in the ranibizumab arm and 1 patient each in the ranibizumab + laser and laser arms. These included 1 case each of myocardial infarction in the ranibizumab and ranibizumab + laser arm, and 1 case of cerebrovascular accident in the ranibizumab arm. At the end of the study, there was no clinically significant difference between treatment arms for either mean BP or IOP, and the values of clinical laboratory evaluations were similar among the study arms (details in Appendix 3, available online at http://aaojournal.org).

Discussion

The results from the RESTORE study demonstrate that treatment with ranibizumab as monotherapy and combined with laser treatment is superior to laser treatment in rapidly improving and sustaining VA in patients with visual im-

Table 12. Adverse Events Potentially Related to Systemic Vascular Endothelial Growth Factor Inhibition (Safety Set)

Preferred Term, n (%)	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5 mg + Laser N = 120	Laser N = 110
Total	14 (12.2)	7 (5.8)	11 (10.0)
Arterial thromboembolic events	6 (5.2)	1 (0.8)	1 (0.9)
Angina pectoris	2 (1.7)	0	0
Pulmonary embolism	2 (1.7)	0	1 (0.9)
Cerebrovascular accident	1 (0.9)	0	0
Myocardial infarction	1 (0.9)	1 (0.8)	0
Hypertension	9 (7.8)	6 (5.0)	9 (8.2)
Non-ocular hemorrhage	1 (0.9)	0	1 (0.9)
Epistaxis	1 (0.9)	0	1 (0.9)
Proteinuria	1 (0.9)	1 (0.8)	0

pairment due to DME. There were no efficacy differences detected between the ranibizumab and ranibizumab combined with laser treatment arms. A greater proportion of patients treated with ranibizumab gained ≥5, ≥10, and ≥15 BCVA letter scores from baseline compared with the laser-treated patients.

Ranibizumab treatment consistently demonstrated significant and superior VA benefit in all subgroups of DME patients, including patients with focal or diffuse DME and those with or without prior laser as compared with laser treatment alone. The functional improvements in BCVA were accompanied by significant improvements in anatomic end points, CRT on OCT, and resolution of leakage on fluorescein angiography. At month 12, 49.1% (ranibizumab), 55.1% (ranibizumab + laser), and 39.1% (laser) patients had CRT <275 μm, whereas 50.9%, 44.9%, and 60.9%, respectively, had CRT >275 μm.

The efficacy results with ranibizumab treatment from the RESTORE study are consistent with the recently published DRCR.net and RESOLVE studies.[9,10] Results from the DRCR.net study showed that ranibizumab used in conjunction with laser therapy (prompt or deferred) was significantly more effective than laser alone in improving VA in patients with DME after 1 year of treatment (+9 [both] vs +3 BCVA letter score; $P<0.001$).[9] In the DRCR.net study, approximately 30% of the ranibizumab + laser patients gained a ≥15 BCVA letter score from baseline compared with 15% of the laser-treated patients.

The RESOLVE study demonstrated that ranibizumab provided rapid and continuous improvements in BCVA compared with sham over a period of 12 months (mean average change in BCVA letter score from baseline to month 12, +7.8 for ranibizumab vs −0.1 for sham; $P<0.0001$).[10] At month 12, approximately 32% of the ranibizumab-treated patients gained a ≥15 BCVA letter score compared with 10% in the sham control arm.

The observed numerical differences in the BCVA outcome between RESTORE and RESOLVE may be partly attributed to the differences in eligibility criteria and as a consequence to baseline characteristics of the enrolled patients. Additionally, the 2 studies had different retreatment criteria, which led to an average of ~10 ranibizumab injections in the RESOLVE study and ~7 injections in the RESTORE study.

Visual impairment or reduced VA adversely impacts patients' independence (activities like reading, interacting socially, watching TV, driving, etc) and HRQoL.[12–14] The RESTORE trial is the first to assess the impact of ranibizumab treatment on HRQoL, particularly using the NEI VFQ-25 questionnaire. Ranibizumab showed progressive and sustained improvements in HRQoL as assessed by the NEI VFQ25 composite scores. The mean change in VFQ-25 composite scores was significant, with ranibizumab monotherapy and combined with laser (5.0 and 5.4 point) versus laser. These results are consistent with those reported for ranibizumab in the neovascular AMD studies Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA), where a 4- to 6-point improvement in mean NEI VFQ-25 scores represented a clinically meaningful change corresponding with a 15-letter improvement in BCVA.[15] The strongest evidence of HRQoL benefit for ranibizumab compared with laser alone was observed for general vision, near, and distance activities NEI VFQ-25 subscales. Adding to the HRQoL outcomes are the data on the proportion of patients who had a BCVA letter score >73 (20/40 Snellen equivalent, the legal minimum for driving in the United States and the United Kingdom) in the study eye at month 12. In RESTORE, at month 12, 44.9% (ranibizumab + laser) and 53.0% (ranibizumab) patients had a BCVA letter score >73 versus 16.1% and 19.8% patients at baseline, whereas with laser 23.6% patients had a BCVA letter score >73 versus 15.3% at baseline. For the EQ-5D scores, none of the differences between the ranibizumab treatment arms and laser arm at any time point were significant. This is not surprising given that EQ-5D does not contain any vision-related domains, and has known ceiling effects,[16] so the scale may lack sensitivity in detecting changes in DME outcomes.

For the TTO scores, the change in mean utility score of 0.13 with ranibizumab was not statistically different from laser alone at month 12 ($P = 0.10$). Results from the TTO utility measurement indicate a numerical improvement with ranibizumab vs laser alone, and hence a possible impact on the quality-adjusted life years associated with ranibizumab therapy.

The RESTORE study used retreatment criteria that were designed to enable an individualized treatment regimen based on patients' disease stability. Patients were assessed monthly to observe disease stability/activity and to guide treatment interruption or reinitiation through changes in VA, supported by clinical and anatomic evaluations attributable to the progression of DME. The validity of this approach was confirmed by the efficacy outcome, which showed that the PRN retreatment regimen could maintain the BCVA gained at the end of the treatment initiation phase. Furthermore, this was achieved with an average of 4 injections in the 9-month continuous/resumed treatment phase. However, it is unknown whether or not VA gains would have been greater if monthly treatment had been maintained over 12 months. Ongoing ranibizumab clinical trials, such as the Ranibizumab Injection in Subjects with clinically significant macular Edema with center involvement secondary to diabetes mellitus (RISE, NCT00473330)[17] and the Ranibizumab Injection in subjects with clinically significant macular Edema with center involvement secondary to Diabetes mellitus (RIDE, NCT00473382)[18] where monthly injections are mandated for 24 months will provide data on maximal VA gains in DME with monthly therapy. Overall, a greater proportion of patients interrupted treatment due to disease stability with ranibizumab than laser (85% [ranibizumab] and 82% [ranibizumab + laser] vs 68%), which was expected because the laser arm received sham injections only. Approximately 33% of the ranibizumab-treated patients interrupted treatment for the first time at month 3 due to treatment efficacy. The proportion of patients with a maximum treatment-free interval of ≥3 months was similar across treatment arms (57.9%–61.9%).

The results from the RESTORE study have assessed the treatment effect of ranibizumab monotherapy in DME, as well as the potential benefit of combining it with laser therapy. Over the 1-year study period, the results from RESTORE show that there were no significant efficacy differences detected between the ranibizumab and the ranibizumab combined with laser treatment arms with respect to improvements in BCVA, as well as the number of injections. Overall, the retreatment criteria based on disease stability used in the RESTORE study allowed a reduction in the number of injections compared with the RESOLVE study, through monthly monitoring to assess patients' need for retreatment.

Ranibizumab as monotherapy or combined with laser was well-tolerated in patients with visual impairment due to DME over 12 months. There were no ocular SAEs observed in the ranibizumab arm. There were no incidences of glaucoma reported in any of the treatment arms and only 1 patient in each ranibizumab arm reported increased IOP. Both cases of IOP increase resolved on their own, without treatment, and the investigator considered these events to be related to injection procedure and not to the drug. Ranibizumab treatment was not found to be associated with an increased risk of cerebrovascular or cardiovascular events in DME patients over 12 months; there were no cases of endophthalmitis reported in the study. The pooled analysis of the 2 pivotal studies, RESOLVE and RESTORE, resulted in an incidence rate of 1.4% for endophthalmitis at 1 year, which is consistent with the incidence rate of 1.6% found in the pooled analysis of the pivotal AMD studies, ANCHOR, MARINA, and PIER (A Phase IIIb, multicenter, randomized, double-masked, sham Injection-controlled study of the Efficacy and safety of Ranibizumab; unpublished data, July 21, 2008). The incidence of AEs potentially related to systemic VEGF inhibition (hypertension, proteinuria, and nonocular hemorrhage) were low and did not differ compared with the laser control cohort. Furthermore, ranibizumab treatment did not negatively influence the VA outcome or the progression of macular ischemia, as confirmed by assessing the BCVA at month 12 in the subgroups with or without the presence of ischemia at baseline, as well as by the degree of capillary loss in the central subfield from baseline to month 12 (Appendix 2, available online at http://aaojournal.org). The safety findings from this study are consistent with the safety profile of other studies with ranibizumab treatment in DME[9,10] and neovascular AMD.[19,20]

In summary, data from the 3 randomized clinical trials RESOLVE, DRCR.net and RESTORE involving >1000 patients provide robust evidence for the efficacy and tolerability of ranibizumab in DME.[9,10] Furthermore, the 24-month results from DRCR.net and the recently published READ-2 study have shown that ranibizumab sustains efficacy[9,11] through year 2 of treatment and was well-tolerated.[9] These reports may lead to a shift in treatment paradigm for DME, from laser, to newer approaches using ranibizumab. Results from the 2-year extension of the RESTORE study will add to the data from studies REVEAL (NCT00989989),[21] RIDE,[18] RISE,[17] and RETAIN (NCT01171976),[22] and DRCR.net (4-year follow-up) and are expected to further enhance the evidence for ranibizumab therapy in DME in the coming years.

In conclusion, RESTORE is the first study to demonstrate that ranibizumab monotherapy provides significantly superior benefit over standard-of-care laser in patients with visual impairment due to DME, rapidly improving and sustaining BCVA over the 12-month treatment period. Ranibizumab therapy was administered using an individualized PRN regimen with monthly monitoring and retreatment based on disease stability. During the 12-month study period combining laser with ranibizumab did not seem to provide any advantage compared with ranibizumab monotherapy in terms of improving BCVA and treatment exposure. However, longer follow-up may be required to assess the benefit of combining laser with ranibizumab. Ranibizumab consistently improved BCVA across all the subgroups of patients, including patients with focal or diffuse DME. Ranibizumab treatment was also associated with progressive and sustained improvements in HRQoL compared with laser alone, as assessed by the NEI VFQ-25 scores. Ranibizumab was well-tolerated in patients with visual impairment due to DME with a safety profile similar to the well-established safety profile in neovascular AMD.[19,20]

References

1. Moss SE, Klein R, Klein BE. Ten-year incidence of visual loss in a diabetic population. Ophthalmology 1994;101:1061–70.

2. Paulus YM, Gariano RF. Diabetic retinopathy: a growing concern in an aging population. Geriatrics 2009;64:16–20.
3. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology 2009;116:497–503.
4. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–806.
5. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 2. Ophthalmology 1987;94:761–74.
6. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115:1447–59.
7. Diabetic Retinopathy Clinical Research Network (DRCR.net). Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol 2009;127:245–51.
8. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480–7.
9. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064–77.
10. Massin P, Bandello F, Garweg J, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 2010;33:2399–405.
11. Nguyen QD, Shah SM, Khwaja AA, et al, READ-2 Study Group. Two-year outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study. Ophthalmology 2010;117:2146–51.
12. West SK, Rubin GS, Broman AT, et al, SEE Project Team. How does visual impairment affect performance on tasks of everyday life? The SEE Project. Arch Ophthalmol 2002;120:774–80.
13. Chia EM, Wang JJ, Rochtchina E, et al. Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 2004;45:71–6.
14. Owen CG, Rudnicka AR, Smeeth L, et al. Is the NEI-VFQ-25 a useful tool in identifying visual impairment in an elderly population? BMC Ophthalmol [serial online] 2006;6:24. Available at: http://www.biomedcentral.com/1471-2415/6/24. Accessed December 20, 2010.
15. Suner IJ, Kokame GT, Yu E, et al. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. Invest Ophthalmol Vis Sci 2009;50:3629–35.
16. Ferreira PL, Ferreira LN, Pereira LN. How consistent are health utility values? Qual Life Res 2008;17:1031–42.
17. Clinicaltrials.gov. Genentech. A study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RISE). ClinicalTrials.gov Identifier NCT00473330. Available at: http://clinicaltrials.gov/ct2/show/NCT00473330. Accessed November 15, 2010.
18. Clinicaltrials.gov. Genentech. A study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RIDE). ClinicalTrial.gov Identifier NCT00473382. Available at: http://clinicaltrials.gov/ct2/show/NCT00473382. Accessed December 20, 2010.
19. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
20. Brown DM, Michels M, Kaiser PK, et al, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration [ANCHOR study 1-year data]. N Engl J Med 2006;355:1432–44.
21. Clinicaltrials.gov. Novartis. Efficacy and safety of ranibizumab (intravitreal injections) in patients with visual impairment due to diabetic macular edema (REVEAL). ClinicalTrial.gov Identifier NCT00989989. Available at: http://clinicaltrials.gov/ct2/show/NCT00989989. Accessed December 20, 2010.
22. Clinicaltrials.gov. Novartis. Efficacy and safety of ranibizumab in two "treat and extend" treatment algorithms versus ranibizumab as needed in patients with macular edema and visual impairment secondary to diabetes mellitus (RETAIN). ClinicalTrial.gov IdentifierNCT01171976. Available at: http://clinicaltrials.gov/ct2/show/NCT01171976. Accessed December 20, 2010.

Footnotes and Financial Disclosures

Originally received: November 3, 2010.
Final revision: January 10, 2011.
Accepted: January 10, 2011. Manuscript no. 2010-1525.

[1] Centre for Vision Research (Westmead Millennium Institute), University of Sydney, Sydney, Australia.

[2] Department of Ophthalmology, University Vita-Salute Scientific Institute, San Raffaele, Milano, Italy.

[3] Universitätsklinik für Augenheilkunde und Optometrie, University of Vienna, Waehringer Guertel, Vienna, Austria.

[4] Division of Medical Retina and Laser Surgery, Department of Ophthalmology, University Eye Hospital Ulm, Ulm, Germany.

[5] Assistance Publique des Hôpitaux de Paris, Ophthalmology Department, Hôpital Lariboisière, Paris, France.

[6] Department of Ophthalmology, Academisch Medisch Centrum Universiteit van Amsterdam, Amsterdam, The Netherlands.

[7] Universitätsspital Zürich, Augenklinik, Nordtrakt II, Zürich, Switzerland.

[8] Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

[9] Novartis Pharma AG, Basel, Switzerland.

Presented in part at: WOC 2010, EURETINA 2010, and AAO 2010.

Appendix 4 contains a list of the primary investigators who participated in this study (available online at http://aaojournal.org).

The authors thank Aditi Gandhe (Novartis Healthcare Private Ltd., India) for her medical writing and editorial assistance and Shivani Mittra (Novartis Healthcare Private Ltd., India) for her contribution toward various drafts of this manuscript.

Financial Disclosure(s):
The authors have made the following disclosures:

P. Mitchell – Novartis – Consultant, Lecturer; Pfizer – Consultant, Lecturer; Allergan – Consultant; Solvay – Consultant; Bayer – Consultant.

F. Bandello – Novartis – Consultant, Lecturer; Allergan – Consultant, Lecturer; Thea – Consultant, Lecturer.

U. Schmidt-Erfurth – Alcon Laboratories, Inc. – Consultant, Lecturer; Bayer Healthcare – Consultant, Lecturer; Novartis – Consultant, Lecturer; Regeneron – Lecturer; Pfizer – Lecturer.

P. Massin – Novartis – Consultant, Lecturer; Allergan – Consultant, Lecturer; Fovea Pharmaceutical – Consultant; Sanofi Aventis – Consultant; Takeda – Consultant, Lecturer.

R.O. Schlingemann – Novartis – Consultant, Lecturer; Bayer Healthcare – Consultant.

F. Sutter – Novartis – Consultant.

G. Burian – Novartis Pharma – Employee.

O. Gerstner – Novartis Pharma – Employee.

A. Weichselberger – Novartis Pharma – Employee.

Sponsored by Novartis Pharma AG, Switzerland. The study is registered with www.clinicaltrial.gov under number NCT00687804.

Correspondence:
Prof. Paul Mitchell, Centre for Vision Research, University of Sydney (Westmead Hospital), Sydney, Australia. E-mail: paul.mitchell@sydney.edu.au.

Lessons Learned From Avastin and OCT–The Great, the Good, the Bad, and the Ugly: The LXXV Edward Jackson Memorial Lecture

PHILIP J. ROSENFELD

• PURPOSE: To describe the synergistic benefits and cost savings from the use of optical coherence tomography (OCT) and vascular endothelial growth factor (VEGF) inhibitors, particularly intravitreal bevacizumab, in the treatment of exudative age-related macular degeneration (AMD).
• DESIGN: Retrospective literature review and personal perspective.
• METHODS: Retrospective literature review and personal perspective.
• RESULTS: The introduction of the first clinically useful OCT instrument coincided with early-phase clinical trials of a drug that would become known as ranibizumab. OCT provided a noninvasive imaging strategy that unambiguously showed the macular fluid associated with exudative AMD and the ability of anti-VEGF therapy to resolve this fluid with concomitant visual acuity improvement. Clinicians came to embrace the use of OCT imaging as the basis for dosing with anti-VEGF drugs, rather than the fixed-interval dosing that was the standard in clinical trials and recommended by industry after approval. But, before ranibizumab was approved for the treatment of exudative AMD, intravenous bevacizumab was approved to treat cancer. Both drugs shared a common molecular lineage, and this led to a clinical trial using intravenous bevacizumab for the treatment of exudative AMD. Intravenous bevacizumab resulted in visual acuity and OCT improvements similar to ranibizumab, and this observation soon led to the intravitreal use of bevacizumab in 2005. Fortuitously, both ranibizumab and bevacizumab were packaged at similar molar concentrations, so similar volumes of both drugs when injected into an eye would result in similar anti-VEGF activity. With ranibizumab not yet commercially available, intravitreal bevacizumab rapidly became adopted worldwide for the treatment of VEGF-driven ocular diseases. Despite numerous attempts by industry and anonymous sources to discredit and prevent its use, bevacizumab spread globally owing to its availability; its low treatment cost, which was $5.50 per 1 mg in the United States; the evidence of efficacy based on OCT imaging and vision improvement; and its perceived safety. In the United States alone, the use of OCT-guided therapy and the use of bevacizumab for the treatment of exudative AMD has saved Medicare over $40 billion since 2008.
• CONCLUSIONS: The rapid adoption of OCT-guided therapy and the use of intravitreal bevacizumab by the global retinal community has prevented blindness from exudative and neovascular ocular diseases worldwide while saving healthcare providers and patients billions of dollars. (Am J Ophthalmol 2019;204:26–45. © 2019 Elsevier Inc. All rights reserved.)

I AM EXCEEDINGLY GRATEFUL TO THE *AMERICAN JOURNAL of Ophthalmology* and the American Academy of Ophthalmology (AAO) for the honor to present the 75th Edward Jackson Award Lecture. My lecture will only cover the first half of my academic career, but this first half has been quite an adventure, covering great and good events, people, and discoveries, as well as several bad and ugly episodes that need to be revealed. In the realm of the great and the good, none of my accomplishments would have been possible without the love and support of my family and the marvelous educators and researchers I've worked with over the years. My story of scientific discovery would have been very different without their confidence in my scientific talents and their trust in my decisions. As an example, after I completed a 9-year MD/PhD program at the Johns Hopkins School of Medicine where I received my PhD in the Department of Molecular Biology and Genetics, my wife supported my decision to switch residencies from Obstetrics and Gynecology to Ophthalmology after completing only 2-1/2 years of clinical training. This career change required a move from Baltimore to Boston in 1991, and this switch was made possible by the academic support of Stuart Fine, who was at the Johns Hopkins School of Medicine at the time. Prior to my residency at the Massachusetts Eye and Ear Infirmary (MEEI), I secured a coveted postdoctoral fellowship with Thaddeus Dryja, where I received a crash course in the field of ophthalmic genetics. This experience led to my interest in the genetics of age-related macular degeneration (AMD), which was greatly influenced during my residency by the research and clinical

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Feb 27, 2019.

From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA.
Inquiries to Philip J. Rosenfeld, Bascom Palmer Eye Institute, 900 NW 17th St, Miami, FL 33136 USA; e-mail: prosenfeld@miami.edu

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2019.02.036

teachings of Johanna Seddon. My research and residency positions also gave me exposure to the ongoing research into optical coherence tomography imaging, photodynamic therapy (PDT) with verteporfin, and vascular endothelial growth factor (VEGF). During the early 1990s, Boston was the epicenter for all 3 breakthrough discoveries. Of note, my indoctrination into VEGF and its vital role in neovascular and exudative ocular diseases was led by my faculty mentors at the time. They included Anthony Adamis, who was my residency director, Joan Miller, Lloyd Paul Aiello, and Lois Smith. It was Lois Smith who recognized my interest in VEGF and its role in exudative AMD, and when I left to pursue a vitreoretinal fellowship and faculty position at the Bascom Palmer Eye Institute (BPEI) in 1995, she provided me with guidance and financial support through the Rasmussen Foundation.

After completing my fellowship at the BPEI and joining the vitreoretinal faculty, I continued my interest in macular degeneration. That decision set me on a course of discovery that involved the use of PDT in clinical trials, optical coherence tomography (OCT) imaging, and anti-VEGF therapies. My familiarity with Joan Miller's PDT research at the MEEI led me to take on the principal investigator's role for the phase 3 PDT clinical trials at the BPEI. That decision took me away from laboratory-based genetic research and into the world of clinical research. Under the tutelage of Neil Bressler, the PDT trials offered me the clinical research training that I was lacking. I was able to then apply my well-honed principles of experimental design to the clinics rather than the laboratory. For those unfamiliar with PDT, this treatment targeted choroidal neovascularization (CNV) by combining the intravenous infusion of a photosensitizing agent with a circular spot of a long-wavelength, nonthermal laser that covered the neovascularization in the macula. As the top-enrolling site in the phase 3 trial, I earned an opportunity to participate in the Food and Drug Administration (FDA) Advisory Panel Meeting in November 1999, which led to the approval of verteporfin PDT in April 2000. From 2000 until 2004, verteporfin PDT was the only approved treatment for exudative AMD, but it was approved for the predominantly classic form of the disease.[1,2] Unfortunately, only a minority of patients would qualify for treatment, and even in these patients, most of them would continue to lose vision even after treatment. In subsequent clinical trials, we modified the approved PDT regimen, but while these changes failed to improve outcomes for the vast majority of patients with exudative AMD, I learned an important lesson. I learned that retrospective subgroup analyses of failed prospective clinical trials are often done in the hope of finding subgroups where the treatment appeared to work, but these retrospective conclusions should never be believed without rigorous testing. After all, history has taught us that these retrospective subgroups will fail when tested in prospectively randomized clinical studies.[3] Improved outcomes for our patients with exudative AMD would have to wait until anti-VEGF therapy was introduced.

THE ANTI-VEGF AND OPTICAL COHERENCE TOMOGRAPHY REVOLUTION

MY SUCCESSFUL ROLE IN THE PDT TRIALS LED TO MY involvement with the early-stage clinical development of rhuFab V2, a humanized antigen-binding fragment directed against all isoforms of VEGF-A. This drug would eventually become known as ranibizumab (Lucentis; Genentech/Roche, South San Francisco, California, USA), which was developed at Genentech by Napoleone Ferrara, one of the "great" contributors described in this lecture. The rhuFab V2 phase 1 study investigators assembled in May 2000 during the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), and we were informed that this drug would be injected intravitreally. At that time, I was skeptical that patients would tolerate frequent intravitreal injections. Despite these reservations, I enthusiastically participated in the phase 1 rhuFab V2 dose escalation study that was initiated in 2001. In this study, patients received a single intraocular injection. After a particular dose was injected into each cohort of at least 6 patients, we assessed the eyes to determine if the dose was safe; and if it was, then we escalated the dose and continued increasing the dose with each cohort until a dose-limiting toxicity was observed. In the phase 1 study, this dose-limiting toxicity was inflammation, and it was observed with the 1.0 mg dose, so the previous dose, which was the 0.5 mg dose, was deemed the maximum tolerated dose.[4] While there was a hint of visual acuity improvement after a single dose, the true benefits of rhuFab V2 would have to wait until the phase 2 study when we performed multiple doses and used of OCT imaging. After all, OCT imaging was not routinely available in the clinics until 2003.

I participated in 2 phase 2 clinical studies.[5,6] The pivotal phase 2 study involved a prospective, sham-controlled randomized trial that investigated monthly dosing of 0.3 mg or 0.5 mg of ranibizumab for 6 months.[5] The lead investigator for that study was Jeffrey Heier of Boston. The second phase 2 study was a 20-week-long open-label dose-escalation trial in which 3 different dosing regimens were tested.[6] I was the lead investigator for this study. The purpose of this dose-escalation study was to determine if we could avoid the inflammation associated with the dose of 1.0 mg by gradually increasing the dose of rhuFab V2. In this study, we escalated the dose to as high as 2.0 mg in some patients. Three different dosing regimens were tried. In the first regimen, subjects were injected every 2 weeks and escalated from 0.3 mg to 1.0 mg; in the second regimen, the dose was escalated every 2 weeks from 0.3 mg to 2.0 mg; and in the

third regimen, the dose was escalated every 4 weeks from 0.3 mg to 2.0 mg. Both phase 2 studies were successful and reported unambiguous visual acuity benefits. In this dose escalation study, we showed that inflammation could be avoided if doses were escalated every 2 weeks or every month. We also showed that injections every 2 weeks were well tolerated, safe, and effective. This observation would later become important when we showed improvement in visual acuity and macular anatomy in some patients when anti-VEGF injections were given every 2 weeks in eyes that were deteriorating with monthly injections.[2] In this paper, we also used pharmacokinetic/pharmacodynamic modeling to support the benefits of more frequent dosing. Another benefit arising from these phase 2 studies was that we obtained the first OCT images of eyes before and after anti-VEGF therapy. This was possible owing to the timely availability of the first clinically useful time-domain OCT instrument, known as the OCT-3 (Stratus OCT; Carl Zeiss Meditec, Dublin, California, USA), which was FDA cleared in 2003. Suddenly, we were at the epicenter of 2 converging revolutionary technologies that would change our management of exudative macular diseases.

The development and commercialization of OCT would not have been possible without the monumental contributions of James Fujimoto, David Huang, and Eric Swanson, then at the Massachusetts Institute of Technology, and their collaborators at the Tufts University New England Medical Center, Carmen Puliafito and Joel Schuman.[3] Carmen Puliafito, my chairman at BPEI in 2003, acquired one of the first OCT-3 instruments, and by imaging subjects in the phase 2 trial, I witnessed the effectiveness of rhuFab V2, now named ranibizumab. For the first time, I saw where the macular fluid was located in eyes with exudative AMD. The fluid could be within the retina, under the retina, and under the retinal pigment epithelium. After an injection of ranibizumab, I observed the resolution of fluid from these compartments. Moreover, the resolution of this fluid correlated with both subjective and objective vision improvement. We also observed that when fluid recurred in some patients a month or more after an injection, the increase in fluid correlated with visual complaints; and when the patient was challenged with another injection of ranibizumab, the macular fluid would resolve, and the vision would improve. I came to appreciate that the OCT would serve as a VEGF-meter, a device that would indicate when excess VEGF was present and when anti-VEGF drug injections were needed.[2]

While OCT imaging revealed the presence and resolution of macular fluid during the phase 2 studies, it wasn't used to determine the need for retreatment, since fixed-dosing intervals were used in both protocols. At that time, there was no question that ranibizumab was effective, but the nagging question was whether monthly injections would be safe and tolerated as a viable long-term treatment strategy. To help address this question and provide

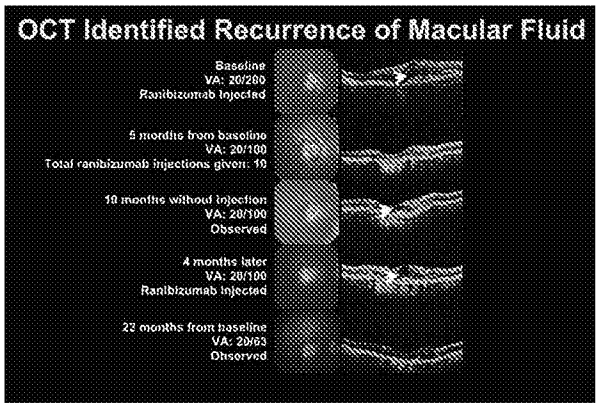


FIGURE 1. Example of a subject treated every 2 weeks with ranibizumab over 5 months in the phase 2 dose-escalation trial and then enrolled in the extension trial that used optical coherence tomography (OCT)-guided retreatment with ranibizumab for an additional 17 months of follow-up. Arrows point to the regions of macular fluid that resolve after ranibizumab treatment and recur following treatment. VA = visual acuity.

ranibizumab for phase 2 study patients once the studies were completed, Genentech was generous in supporting an open-label extension trial in which all subjects could roll over from the phase 2 studies into a long-term study that provided 0.5 mg ranibizumab for all patients until the drug was approved. The most notable feature of this extension-study protocol was that Genentech, at our request, did not require monthly dosing. Once the phase 2 study was completed, Genentech heeded our request to allow as-needed dosing based on the investigator's discretion. This was the perfect scenario in which to observe the durability of the ranibizumab therapy, determine whether monthly dosing was really needed, and assess whether OCT-guided therapy could maintain the visual acuity gains and OCT outcomes following the phase 2 fixed-interval dosing regimen with ranibizumab (Figure 1). At our center, 23 subjects were followed for over 18 months after completing the phase 2 studies. During this time, OCT imaging was performed on all patients. We found that the visual acuity gains were maintained in all patients and 7 patients did not need another injection based on OCT imaging. For those patients needing another injection, the median time to injection was 196 days, and the median number of reinjections at 12 months was 6, and at 18 months the median number of injections was 10. These data were presented at the 2004 Retina Subspecialty Day meeting during the annual meeting of the AAO. At the time, my colleagues did not believe that OCT alone was all that was needed to decide retreatment. After all, fluorescein angiography was still the gold standard for determining leakage from macular neovascularization. At the time, my hope was that I could publish these results in 2004, but Genentech felt that our patients represented only a subset of the total number of patients in the phase

2 extension study and could not be independently reported. These results from the phase 2 extension study were never published.

By this time, I was confident that OCT-guided therapy was the future for the management of exudative AMD with anti-VEGF therapy, and with the support of Stephen Judd and Ram Palanki at Genentech, we designed a clinical study in 2003 that became Genentech's first investigator-sponsored trial in ophthalmology. This investigation was a prospective, open-label clinical study named the Prospective Optical Coherence Tomography (OCT) Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Lucentis™ (PrONTO) Study (FDA Investigative New Drug (IND) #11715). The protocol was approved by the institutional review board (IRB) of the University of Miami (UM) Miller School of Medicine. The study design required that we follow patients monthly and re-treat based on the detection of macular fluid by OCT imaging. At that time, Anne Fung was my medical retina fellow, and the study would not have been possible without her expertise and assistance. Eventually, this OCT-guided approach would become known as treat-and-observe.[10,11]

THE PrONTO STUDY AND OPTICAL COHERENCE TOMOGRAPHY–GUIDED RETREATMENT

THE PRONTO STUDY ENROLLED AND FOLLOWED 40 PATIENTS every month for 2 years. To convince the skeptics that OCT-guided therapy could replace fixed-interval dosing, we treated monthly until the macula was dry and then we used retreatment guidelines during the first year of the study that we knew allowed for too much fluid to reaccumulate before we reinjected. Our intention was to demonstrate to the naysayers that when a small amount of fluid accumulated, if left untreated, then even more macular fluid would accumulate and vision would deteriorate. For that reason, we tolerated the accumulation of up to 100 μm of central macular fluid before retreatment was offered. Another indication for retreatment was the appearance of any new macular hemorrhage at any of the monthly visits. However, an enlarging retinal pigment epithelial detachment was not an indication for retreatment during the first year. As a concession to Genentech, we agreed to their mandate that all subjects receive 3 monthly injections to start the study before OCT-guided retreatment was initiated. As a result, these 3 monthly injections to start an anti-VEGF study have become a fixture in all subsequent industry-sponsored studies, especially those trials using OCT-guided therapy or any dosing that is less frequent than every month. At the time, there were no data to support this 3-monthly-injection requirement.

After the first year of the PrONTO Study, more than 95% of eyes were fluid free after the first 3 injections and the mean visual acuity improvement at the end of the year was 9.3 letters, which was very similar to the outcomes reported from monthly ranibizumab injections in the phase 2 study. However, visual acuity did fluctuate depending on whether fluid reaccumulated; however, vision improved once the reinjections were given. As expected, the vision improvements mirrored the OCT improvements. On average, only 5.6 injections were needed during the first year, compared with the 12 injections that would be given using a fixed-monthly dosing regimen. Moreover, we proved that when any macular fluid reaccumulated, then more fluid would follow. For that reason, in the second year of the study, the retreatment criteria were changed so that any reaccumulation of macular fluid would trigger a retreatment. Not only did we adopt a "no macular fluid" policy, but we also modified the protocol so that any unambiguous qualitative increase in the height of a pigment epithelial detachment, as determined by me, would be sufficient to trigger a retreatment. After 24 months, there was a mean visual acuity improvement of 11.1 letters with an average of only 9.9 injections. By every metric, the PrONTO study was a resounding success and established OCT imaging as the gold standard for deciding when to re-treat when using anti-VEGF therapy. While the scientific rigor of the study would have benefited from a control arm that received monthly injections, the results ended up being so definitive that few doubted the significance of the study. It should be noted that at that point in time, the FDA did not require a randomized control arm in a phase 2 study, but it is my understanding that if the PrONTO Study were repeated today, the FDA would mandate a control arm to the study.

As a result of PrONTO, numerous other OCT-guided retreatment studies were initiated, with many of them using the 100-μm rule for retreatment even though it was discarded after the first year of the PrONTO study. Results from these follow-up studies were variable primarily because they failed to follow rigorous monthly follow-up and retreatment guidelines. However, the PrONTO Study was fully validated by a large randomized clinical study known as the "pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration (HARBOR) study."[12,13] In Genentech's HARBOR Study, OCT-guided therapy was compared with monthly dosing of ranibizumab. In the arm with OCT-guided therapy, all subjects started with 3 monthly injections, followed by monthly visits with OCT imaging, and ranibizumab retreatment was given with the recurrence of any fluid on OCT imaging.

Another OCT-guided retreatment strategy that has gained popularity is known as treat-and-extend, in which anti-VEGF injections are given at every monthly visit until the macular fluid has resolved, and once the macular fluid is

gone, an injection is given and the treatment interval is then slowly extended, usually by 2 weeks.[2,14] Even if the fluid is absent at any given visit, an injection is given and the follow-up interval is increased by 2 weeks again; but if fluid recurs, an injection is given and the interval is then shortened by 2 weeks. Although variations of this strategy have been reported, the overall objective is to decrease the burden of monthly visits; but this convenience is offset by a potential increase in the overall number of injections compared with a pure OCT-guided treat-and-observe strategy (but still fewer injections than a fixed-monthly injection regimen). Both treat-and-observe and the treat-and-extend strategies are clinically useful depending on whether a patient prefers to avoid an injection or whether a patient would rather avoid frequent monthly visits. In the 2017 Patterns and Trends Survey sponsored by the American Society of Retina Specialists, OCT-guided therapy in some form was used by over 98% of injecting clinicians worldwide, which validates the significance of my original clinical observations from the ranibizumab phase 2 extension study, and, to the credit of Genentech, demonstrates the global significance of the investigator-sponsored trial known as the PrONTO study, which would not have been possible without Genentech's support.

While ranibizumab was being studied in phase 1/2 clinical trials, another VEGF inhibitor known as pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, New York, New York, USA) was being developed.[15] This drug, which is a RNA oligonucleotide known as an aptamer, inhibited VEGF-A, but only the isoforms that were 165 kDa or larger. Pegaptanib sodium was FDA approved in December 2004 and became commercially available in January 2005, about 18 months before ranibizumab would be approved, and about a year after bevacizumab had been approved for the intravenous treatment of colorectal cancer.[16–18] One of the reasons why pegaptanib sodium was able to beat ranibizumab to market was because they elected to bypass a traditional prospective, randomized, multidose phase 2 study and go directly from their phase 1 study to a phase 3 study. However, this tradeoff came at a price. They sacrificed potential efficacy for expediency. In the phase 1 study, Eyetech dosed their drug every 4 weeks; but in the phase 3 study, they elected to dose their drug every 6 weeks. We can only assume that they believed the intravitreal injection would be better tolerated if it was given less frequently, and they boldly extended the treatment interval without any clinical data. While the results were good enough to get FDA approval, the real-world experience with pegaptanib was less than satisfying. Eventually, both clinicians and patients would conclude that pegaptanib was less effective than either bevacizumab or ranibizumab for treating exudative AMD, and this lack of efficacy was probably due to the extended 6-week dosing interval and the inability of pegaptanib to inhibit all isoforms of VEGF-A.[19] Perhaps, if Eyetech had taken the time to incorporate OCT imaging in their phase 2 clinical trial design, they probably never would have extended the treatment interval to 6 weeks. Moreover, for those of us with the ability to image patients with OCT, it became unambiguously obvious that pegaptanib did not dry the macula after an injection in most patients. This experience provided the first evidence that OCT could be used to distinguish the efficacy of different anti-VEGF drugs. Moreover, it proved to be a crucial observation that led to the rise of bevacizumab and the demise of a pegaptanib sodium.

THE RISE OF SYSTEMIC BEVACIZUMAB

IN 2003, THE PHASE 3 TRIAL WITH RANIBIZUMAB WAS JUST getting started and the pegaptanib phase 3 trial was well underway. Both of these studies used fixed-interval intravitreal dosing; ranibizumab was given every 4 weeks and pegaptanib every 6 weeks. At that time, there was only 1 study that used anti-VEGF therapy guided by OCT imaging, and that was the PrONTO Study. However, we were designing another study that would use both anti-VEGF therapy and OCT imaging. This investigation became known as the Systemic Avastin for Neovascular AMD (SANA) Study.[20,21] The idea of using systemic bevacizumab came about from my exposure to ranibizumab in the phase 1/2 clinical studies, from my experience using OCT to image subjects in the ranibizumab extension trial, and from my experience with the PrONTO Study. Since there was quite a bit of uncertainty about whether patients would tolerate repeated intravitreal injections and whether these injections were safe for the long term, I was attracted to the idea of giving a systemic drug to treat exudative AMD. By giving a systemic drug, I reasoned that a single infusion could treat both eyes, which was appealing given that many patients had bilateral exudative disease, and that repeated systemic infusions were thought to be safer than repeated intravitreal injections. But, what about the increased risk of thromboembolic events from the use of systemic bevacizumab? That risk wasn't fully appreciated until 6 months after bevacizumab was approved in February 2004. Thus, in 2003 the idea of systemic anti-VEGF therapy seemed reasonable, but we didn't know whether systemic bevacizumab would be able to get into the back of the eye and have effects that were similar to an intravitreal injection of ranibizumab in eyes with exudative AMD. After all, bevacizumab and ranibizumab were thought to be very different anti-VEGF drugs. We also didn't know the right dose or the right dosing interval. However, by reviewing the literature, we subsequently learned that Genentech was guarding a secret.

To Genentech's credit, they encouraged their scientists to publish the research that led to the development of ranibizumab and bevacizumab, which included their cloning of

the gene that encoded the VEGF-binding domain for both ranibizumab and bevacizumab, as well as the crystallography of this VEGF-binding domain.[22] Based on the published literature, I realized that both drugs were developed from the same genetic sequences or plasmid clones that were engineered from the murine anti-VEGF monoclonal antibody developed at Genentech. The VEGF-binding domain, also known as the antigen binding fragment (Fab), derived from this murine clone was subsequently humanized by replacing certain amino acid coding regions. In the case of bevacizumab, 2 of these humanized VEGF-binding domains (Fabs) were attached to a humanized Fc fragment to construct a humanized full-length antibody against VEGF. In the case of ranibizumab, the genetic sequence was mutagenized and underwent a process called affinity maturation to identify sequences that would bind VEGF with a higher affinity compared with the original Fab. The affinity-matured Fab contained 6 amino acid changes, with 4 of the changes being responsible for a higher affinity for VEGF, roughly a 100-fold increase in inhibitory activity. A higher affinity for a single Fab was needed because, unlike bevacizumab, which would have 2 binding domains attached to a single Fc arm, ranibizumab would have a single binding domain; thus a higher affinity would be needed for comparable molar inhibition of VEGF. So, why did Genentech go to all the trouble of developing 2 different drugs when we now know that bevacizumab could have sufficed as an intravitreal treatment for exudative AMD?

In retrospect, the answer to this question now seems obvious, but at the time there was a great deal of uncertainty as to whether a full-length antibody could penetrate the retina and be effective in treating subretinal neovascularization when injected into the vitreous, and Genentech had no interest in pursuing a systemic treatment for exudative AMD. The clinical researchers at Genentech were directed to develop bevacizumab for systemic cancer therapy and ranibizumab for the intravitreal treatment of neovascular and exudative eye diseases. However, while I was involved in the ranibizumab trials, I learned that bevacizumab would be commercially available long before ranibizumab would be approved. Moreover, I found the idea of an intravenous infusion rather than an intravitreal injection particularly attractive, and after talking with my patients, I came to believe that some would prefer an intravenous infusion over an intravitreal injection. As a result, I approached Genentech and asked my contacts on the ranibizumab development team whether they would consider a study using systemic bevacizumab. Since their job was the successful commercialization of ranibizumab for the eye, they had no interest in pursuing systemic bevacizumab for the eye. When I was directed to the bevacizumab development team, I got a similar response, only their focus was the successful commercial development of systemic bevacizumab for cancer therapy, not the eye. Each of these drug development teams were siloed into their respective missions, and no one at Genentech was interested in pursuing systemic bevacizumab for the eye.

After my discussions with Genentech, I took the initiative and designed a clinical study that was very similar to the PrONTO study. However, instead of using intravitreal ranibizumab, I used intravenous bevacizumab. Instead of using 3 monthly injections of ranibizumab, I used 3 infusions of bevacizumab at the dose and dosing interval that were used in the bevacizumab phase 3 cancer protocols. In these cancer protocols, bevacizumab was given every 2 weeks at a dose of 5 mg/kg. As in the PrONTO study, I followed the patients in the SANA Study closely with OCT imaging and OCT-guided retreatment was followed after the first 3 infusions. However, in the SANA Study, I modified the requirement that the study start with 3 doses, and I allowed the third dose to be withheld if there was no evidence of macular fluid by OCT. After all, the SANA Study was my study and the 3 doses were not being mandated by Genentech. The SANA Study also differed from the PrONTO study by including indocyanine green angiography as well as fluorescein angiography. After the initial 2 doses, the patients would be followed every 2 weeks with OCT-guided therapy and retreatment was continued if any macular fluid persisted or recurred.

So how did I pay for this systemic bevacizumab study, given the fact that Genentech wasn't interested in supporting my research? My chairman at the time, Carmen Puliafito, allowed me to raise $200,000 from grateful patients to support the study. The plan was to enroll patients with refractory exudative AMD into this open-label prospective study, follow them every 2 weeks for a total of 6 months, and perform OCT imaging at every visit and dye-based angiography every 3 months. The study was approved by the IRB of the University of Miami Miller School of Medicine, and we were not required to submit an FDA Investigational New Drug (IND) application because we were not changing the safety profile of the drug, since we used the FDA-approved dose, dosing interval, and route of administration, we had no intention of seeking a change in the drug's label, and we had no intention of marketing the drug for this off-label indication.[23] We obtained IRB approval prior to the FDA approval of bevacizumab, so when bevacizumab was FDA approved and became commercially available in February 2004, the study was initiated with the help of Stephan Michels, my research fellow at the time. Both Stephan and Andrew Moshfeghi, my medical retina fellow, played pivotal roles and greatly contributed to the success of this study.

After the first infusion of bevacizumab in all patients, the OCT response was truly remarkable, with an overall improvement in vision and macular anatomy after 3 months.[20] In fact, the responses were very similar to the responses observed after an intravitreal injection of

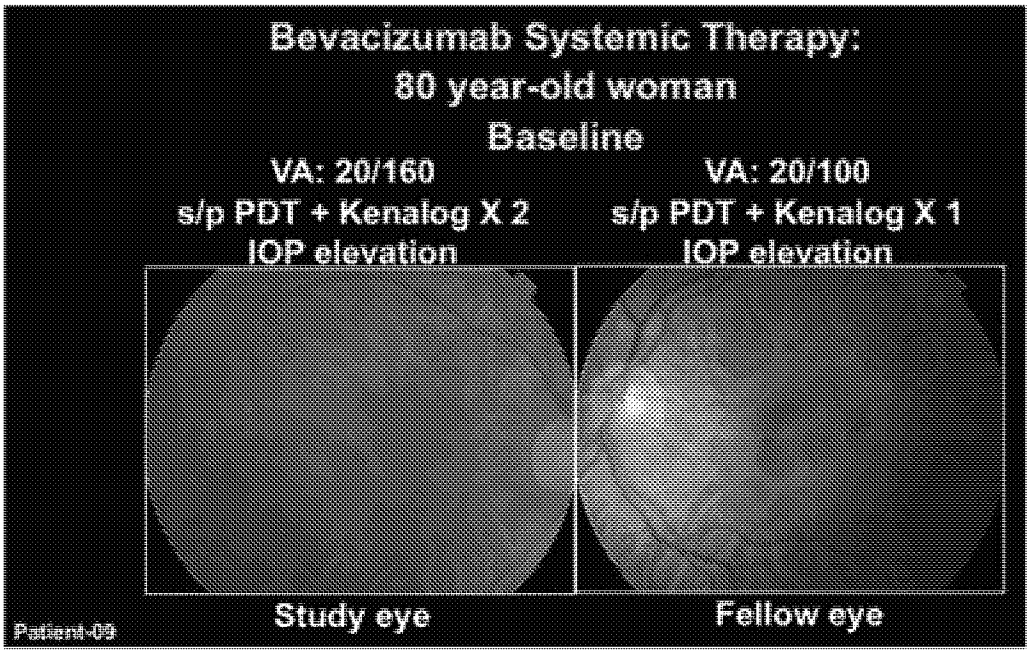


FIGURE 2. Baseline color fundus images from a subject enrolled in the Systemic Avastin (Bevacizumab) for Neovascular Age-Related Macular Degeneration (SANA) trial. IOP = intraocular pressure; PDT = photodynamic therapy; VA = visual acuity.

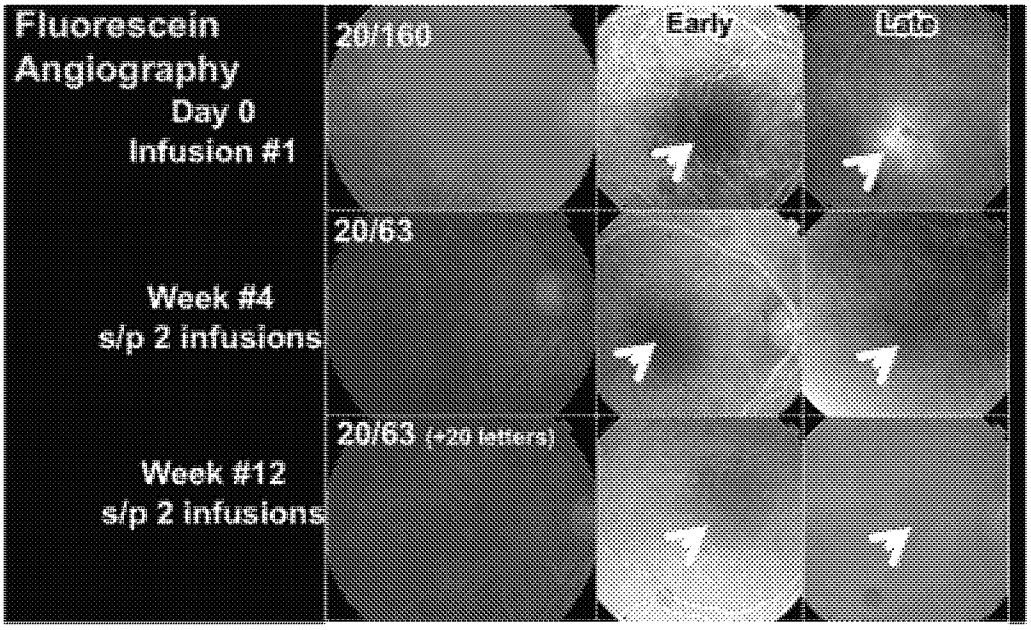


FIGURE 3. Early and late fluorescein angiographic images of the right eye (study eye) from the subject in Figure 3 at baseline and 4 weeks and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The fluorescein leakage (arrow) seen at baseline was absent by the 4-week follow-up.

ranibizumab. Within 24 hours, OCT imaging revealed dramatic improvements in the amount of macular fluid. A total of 18 patients were enrolled, and 16 of these subjects had bilateral exudative AMD (Figures 2-8). Of the 18 patients enrolled, a dry macula was achieved in 11 subjects after only 2 infusions and 7 subjects after 3 infusions, and these infusions were given at 2-week intervals during the first 6 weeks of the study. Retreatment was only offered if macular fluid recurred based on OCT imaging. By 24 weeks, retreatment was needed in 6 of the 18 study eyes. In the

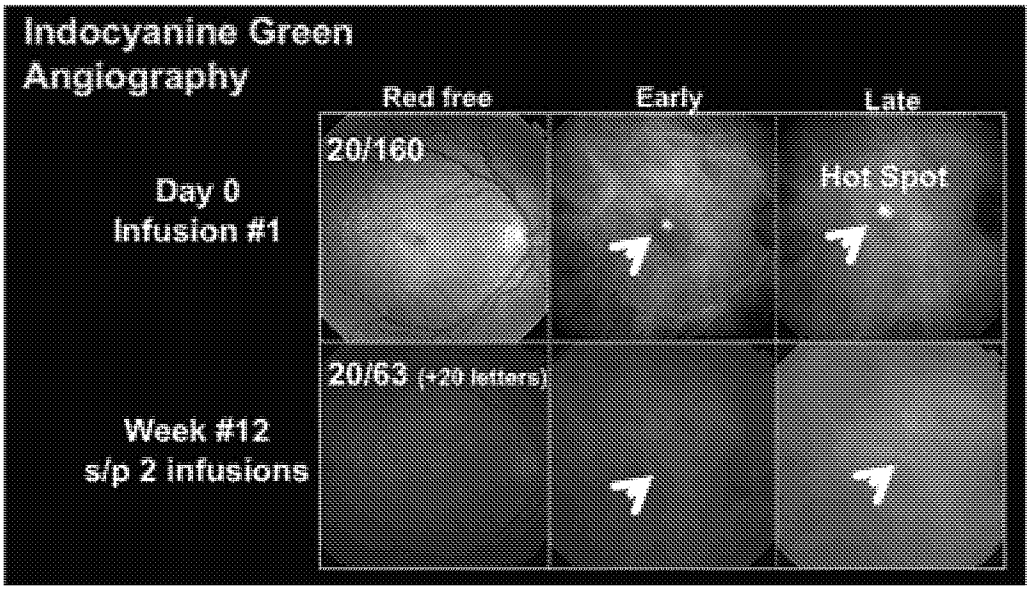


FIGURE 4. Early and late indocyanine green angiographic images of the right eye (study eye) from the same subject as in Figure 3 at baseline and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The hot spot (arrow) seen at baseline was not detectable by the 12-week follow-up. This neovascular lesion appeared consistent with type 3 macular neovascularization, which is consistent with the optical coherence tomography images in Figure 6.

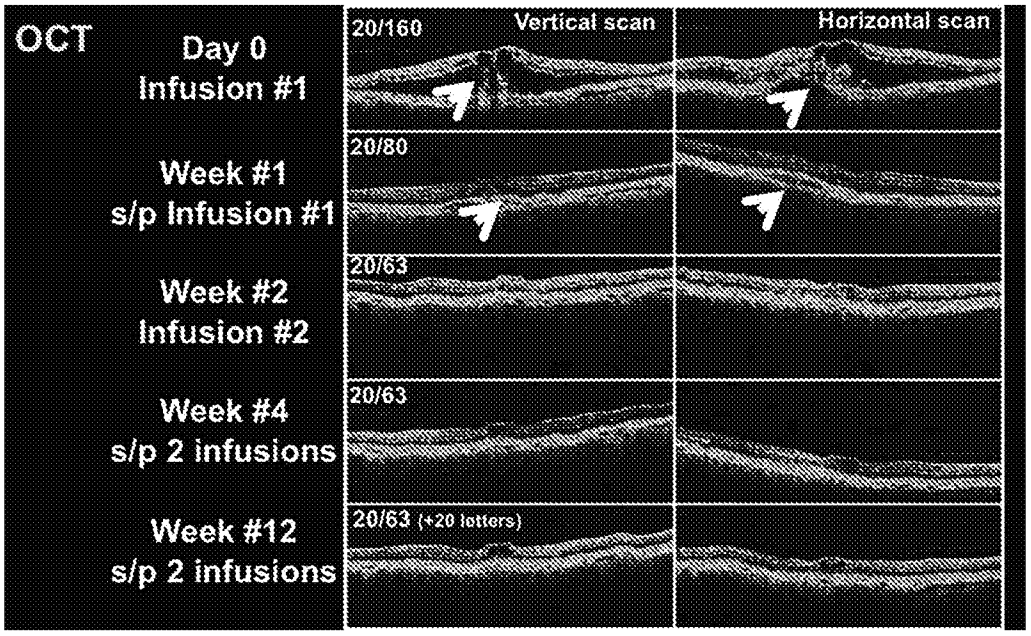


FIGURE 5. Vertical and horizontal optical coherence tomography (OCT) B-scans of the right eye (study eye) from the same subject as in Figure 3 showing cystic maculopathy and a retinal pigment epithelial detachment (PED) at baseline (arrow) consistent with type 3 macular neovascularization. One week after the first infusion of bevacizumab, the cystic maculopathy had resolved, and by 2 weeks the PED had mostly resolved as well. Twelve weeks after baseline and 2 bevacizumab infusions, the subject had gained 20 letters of vision.

study eyes, vision improved by an average of 14 letters and in the nonstudy fellow eyes, vision improved by 17 letters. Vision improvement coincided with an improvement in OCT macular fluid, and all results were highly statistically significant ($P \leq .001$). The only systemic adverse event during the course of the study was a mild increase in systemic blood pressure in 10 of the 18 subjects, with mean increases of 11 mm Hg and 8 mm Hg in the systolic blood pressure

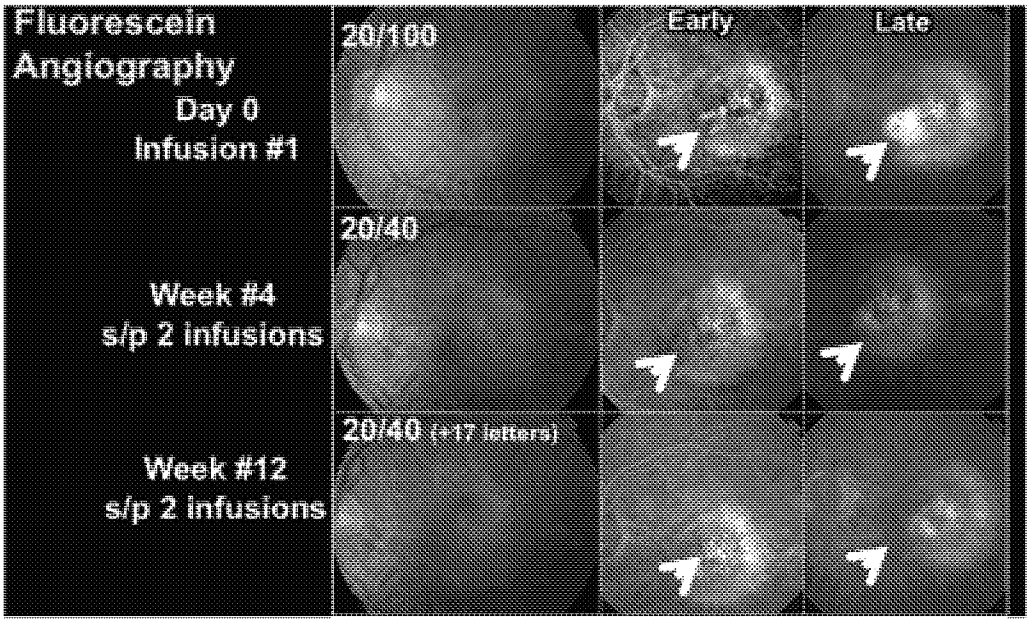


FIGURE 6. Early and late fluorescein angiographic images of the left eye (fellow eye) from the same subject as in Figures 3 through 6 at baseline and 4 weeks and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The fluorescein leakage (arrow) seen at baseline had decreased by the 4-week follow-up. Of note, the leakage arising from the classic (type 2) neovascular component appeared to resolve over 12 weeks.

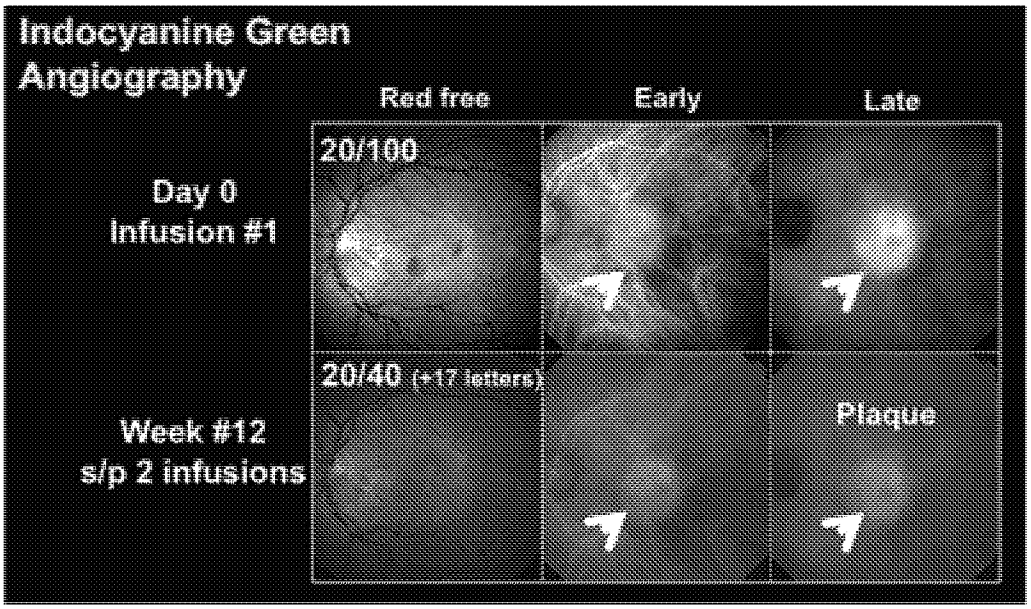


FIGURE 7. Early and late indocyanine green angiographic images of the left eye (fellow eye) from the same subject as in Figures 3 and 7 at baseline and 12 weeks after enrollment into the systemic bevacizumab study. The subject received 2 infusions of systemic bevacizumab at baseline and then 2 weeks later. The plaque (arrow) seen at baseline less intense by the 12-week follow-up. This neovascular lesion appeared consistent with occult or type 1 macular neovascularization, which is consistent with the optical coherence tomography images in Figure 9.

and diastolic blood pressure measurements, respectively. By 24 weeks, our internists had controlled the blood pressure elevations, and all patients ended the study with lower blood pressure measurements compared with their baseline measurements. Unlike the cancer studies, there were no thromboembolic events and no episodes of proteinuria or bleeding diatheses; however, our sample size was small. We only studied 18 patients over 6 months.

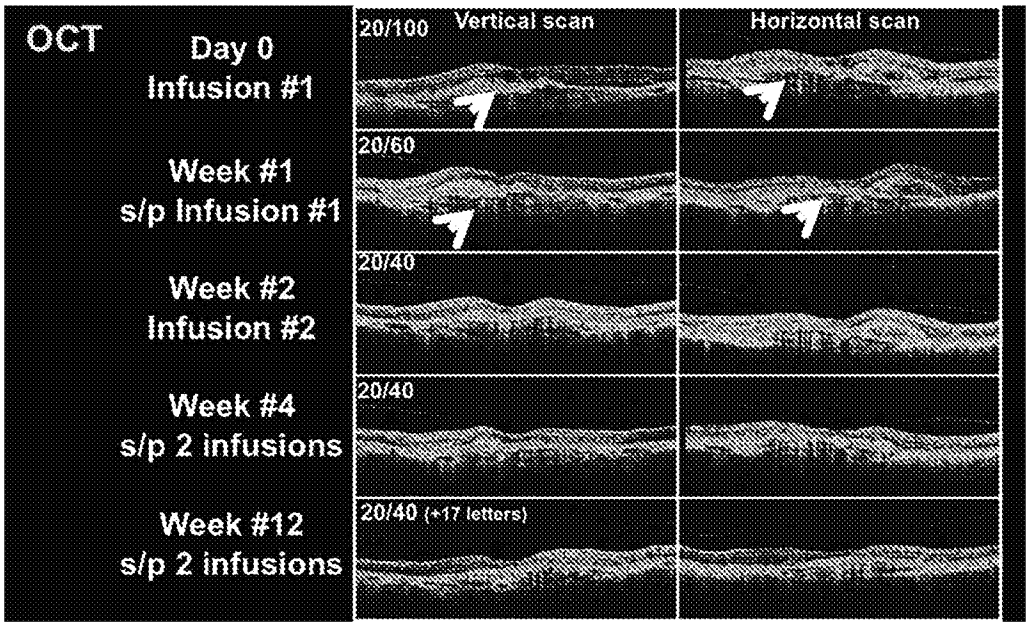


FIGURE 8. Vertical and horizontal optical coherence tomography (OCT) B-scans of the left eye (fellow eye) showing a low-lying retinal pigment epithelial detachment (PED) with subretinal hyperreflective material (SHRM) at baseline (arrow) consistent with a combined type 1/2 macular neovascular lesion. By 12 weeks after baseline following 2 bevacizumab infusions, there was significant resolution of the macular fluid and SHRM, and the subject gained 17 letters of vision.

Overall, the SANA Study was a resounding success. In contrast to the cancer patients receiving intravenous bevacizumab, it appeared as though exudative AMD patients required far fewer treatments, between 2 and 4 treatments over 6 months, with additional treatments probably needed every 3 months. This would result in a total of 4 to 6 infusions over 1 year. With an average cost for a single infusion of bevacizumab at $2200 per dose, the annual cost for systemic bevacizumab therapy would be roughly $13,200. By comparison, the average patient in PrONTO received about 6 injections of ranibizumab the first year. Once ranibizumab would be approved, the cost per injection was about $2000, so the annual costs for systemic bevacizumab and intravitreal ranibizumab would be roughly equivalent per eye, but since systemic bevacizumab would cover both eyes, the use of systemic bevacizumab would be more cost-effective. Moreover, patients wouldn't need to undergo intravitreal injections.

By the summer of 2004, my chairman and I paid our own way out to Genentech to present our preliminary data from the SANA Study. In a conference room on the Genentech campus, we met with Susan Desmond Hellman, Napoleone Ferara, Hal Barron, and the clinical leadership from Genentech. When we showed them our results, they were flabbergasted and promised to help us. Despite numerous attempts to engage with them after that visit, they refused to speak to us ever again about systemic bevacizumab for the treatment of exudative AMD.

By late 2004, the 12-week results from SANA were available and a manuscript was written, but 2 journals rejected our paper without criticizing the research. The editors felt that our conclusions were too radical at the time, and they were concerned about the widespread use of off-label intravenous bevacizumab if they published the research. Only Andrew Schachat, the editor of the journal *Ophthalmology*, had the courage to publish our results. A report on the first 9 patients followed for 3 months was published in the June 2005 issue of *Ophthalmology*,[20] and a second a scientific paper describing all 18 patients followed through 6 months was presented at the annual meeting of the AAO in October 2005 and subsequently published in *Ophthalmology* in 2006.[21] However, news of our results began to spread throughout the vitreoretinal community before the research was published. After all, it was late 2004, it appeared as though we had an effective therapy, bevacizumab was commercially available, and ranibizumab was still 18 months away from approval. However, the treatment landscape was about to change with the approval of pegaptanib sodium in December 2004. Beginning in January 2005, pegaptanib became commercially available, and the intravitreal injection of pegaptanib became the first-line treatment for all patients with exudative AMD.

With the availability of pegaptanib, the urgent need for systemic bevacizumab receded and our unbridled enthusiasm for intravenous bevacizumab as a treatment was tempered because in August 2004, the FDA issued a black

box warning for systemic bevacizumab. This black box warning was issued 6 months after the approval of bevacizumab and 6 months after the SANA Study was initiated. The black box warnings described increased risks of gastrointestinal perforations, wound healing complications, hemorrhage, and thromboembolic events from the use of intravenous bevacizumab. At the time, it was important to remember that in the cancer trials, bevacizumab was dosed every 2 weeks without interruption in combination with more traditional chemotherapy, and this therapy was initiated after surgery to resect the cancer. As a result, it was unclear if our AMD patients were at the same risk; however, our patients were older than the typical patients with colorectal cancer. Immediately after the FDA warnings were issued, our patients in the SANA Study were informed and our IRB-approved consent was revised to include these warnings. All patients in the SANA Study were then re-consented. Even after this new warning, none of our subjects dropped out of the SANA Study, there were no thromboembolic events, and all the subjects ended the study with better vision than when they started the study. Overall, the SANA Study was a great success, but the study wasn't powered to show if the treatment was truly safe. If we wanted systemic bevacizumab to become first-line therapy for exudative AMD, then we needed to perform a larger, multicenter, prospective, sham-controlled clinical trial.

THE RISE OF INTRAVITREAL BEVACIZUMAB

BY MID-2005, WE WERE READY TO RUN A LARGE MULTIcenter clinical trial for the study of systemic bevacizumab in exudative AMD. On Sunday, May 1, 2005, we held an invitation-only organizational breakfast meeting for about 50 prominent retina specialists at the Marriott Harbor Beach Hotel during the annual ARVO meeting in Fort Lauderdale, Florida. We presented the treatment outcomes from the SANA Study. The presenters included Anne Fung, Stephan Michels, Andrew Moshfeghi, and me. In addition, our internists, Erin Marcus and Joshua Lenchus, presented the safety data. Everyone was impressed by the visual acuity and imaging data, but our retina colleagues were concerned about the risk of thromboembolic events, even though we experienced none of the serious adverse events. The attendees wanted to see if we could achieve similar efficacy with a lower systemic dose, which should translate into safer dose of intravenous bevacizumab. We were disappointed. We thought there would be unbridled enthusiasm for systemic bevacizumab, but instead we were instructed to find the lowest, most effective dose of systemic bevacizumab for exudative AMD.

During the week after ARVO, I was in the process of designing a clinical trial using a lower systemic dose of bevacizumab when I had a eureka moment while going through my calculations. I realized that the commercially available bevacizumab had the same molar concentration as the high-dose solution of ranibizumab being used in the PrONTO Study and the ongoing phase 3 ranibizumab clinical trials. Bevacizumab was supplied in a preservative-free buffered solution (pH 6.2) at a concentration of 25 mg/mL. Ranibizumab was supplied in a preservative-free buffered solution (pH 5.5) at a concentration of 10 mg/mL. With the molecular weight of bevacizumab (149 kDa) being about 3-fold greater than the molecular weight of ranibizumab (48 kDa) and the commercial concentration (mg/mL) of bevacizumab being 2.5-fold greater than ranibizumab, I suddenly realized that both drugs had similar molar concentrations. That meant a similar volume of both drugs would contain a similar number of molecules or a similar amount of VEGF-binding activity. As a result, a volume of 0.05 mL, which was the standard volume used for a ranibizumab injection, and a 0.05 mL volume of bevacizumab would contain the equivalent amount of VEGF inhibitory activity. This realization that the same volume of bevacizumab, right out of the bottle, could be equivalent in terms of VEGF binding activity when compared to the same volume of ranibizumab was a startling fact based solely on serendipity. Genentech just happened to package both ranibizumab and bevacizumab at similar molar concentrations. The other remarkable conclusion was that this dose of bevacizumab, which was 0.05 mL of a 25 mg/mL solution, resulting in a dose of 1.25 mg, would cost under $7, since the per-milligram cost of bevacizumab was $5.50/mg. In comparison, once ranibizumab was approved, a similar dose would cost $2000 and the per-milligram cost of ranibizumab would be $4000/mg. However, there were other considerations that needed to be addressed.

When I had my epiphany, I was confident that an intravitreal injection of bevacizumab would be safe based on my experience with ranibizumab and the composition of bevacizumab buffer excipients. At the time, I didn't know if a molar-equivalent dose of bevacizumab would be as effective, more effective, or perhaps less effective than ranibizumab. Since bevacizumab was a full-length antibody with 2 VEGF-binding sites per molecule and a larger molecular weight compared with ranibizumab, I thought it would bind more VEGF and have a longer half-life in the eye, and thus show greater treatment durability. However, each VEGF-binding site on a molecule of bevacizumab had a VEGF binding affinity that was 140-fold lower than the ranibizumab Fab. But, the greatest unknown was whether bevacizumab, which was a full-length antibody, would even penetrate the retina after an intravitreal injection, or whether retinal penetration was even necessary. After all, it was believed that the VEGF causing the neovascularization was located under the retina, and one of the reasons Genentech developed ranibizumab was to provide a small molecule that could more easily penetrate

the retina. But what if bevacizumab could bind VEGF in the vitreous and the vitreous could serve as a sink to draw VEGF out of the retina? If that were the case, then inhibition of vitreal VEGF would suffice.

Upon review of the literature, several important animal studies came to light. In 1996, Adamis and associates published a paper showing that multiple, intravitreal injections of a bevacizumab-like molecule from Genentech inhibited the formation of iris neovascularization in a monkey model of neovascular glaucoma and no drug-related adverse events were observed.[24] While this model showed that the injection of an antibody could be tolerated, the efficacy of this antibody only required intravitreal inhibition of VEGF. To address the question of whether a full-length antibody could penetrate the retina, Genentech scientists performed a study to compare the retinal penetration of an antibody with a Fab in male Rhesus monkey eyes.[25] In this study, they used a recombinant humanized monoclonal antibody (Mab) against HER2, known commercially as Herceptin, and a recombinant humanized Fab against VEGF, which was similar to ranibizumab. They showed that the antibody had a longer half-life (5.6 days) compared with the Fab (3.2 days). They also showed that the full-length antibody failed to penetrate the retina while the Fab easily penetrated the retina. Thus, they used this evidence to support the development of ranibizumab for the eye rather than bevacizumab. However, this study was flawed. Instead of using a bevacizumab-like antibody, they used an antibody that recognized HER2, and the HER2 antigen was present in the inner retina.[26] In their experiment, the full-length antibody couldn't penetrate the retina from the vitreous, but it wasn't because the antibody was too large; it was because the antibody became bound to HER2 and couldn't penetrate into the retina from the vitreous. A subsequent paper in 2004 by Dennis Han did show that full-length antibodies could penetrate the retina.[27] Thus, in May of 2005, it was perfectly reasonable to conclude that an injection of bevacizumab, at a dose equivalent to ranibizumab, could penetrate the retina and be used to treat exudative AMD. However, even if it couldn't penetrate the retina, bevacizumab could inhibit VEGF in the vitreous and the proposal that the vitreous could serve as a VEGF sink to draw VEGF out of the retina down its concentration gradient seemed reasonable.

The timing of the bevacizumab breakthrough couldn't have been better for patients. In early May 2005, our only treatments were pegaptanib and verteporfin PDT. While verteporfin PDT was approved for only a minority of eyes with predominantly classic CNV, pegaptanib was approved for all eyes with exudative AMD. However, after using pegaptanib for the treatment of exudative AMD over the 5 months of commercial availability from January to May 2005, we found that the average patient continued to lose vision, and OCT imaging revealed persistent or increasing amounts of macular fluid in these patients. Our patients were deteriorating, and I knew ranibizumab would be superior to pegaptanib based on our previous studies, but ranibizumab would not be available for another 14 months. My options were to continue to inject pegaptanib every 6 weeks at a drug cost of $1650 per dose and watch my patients lose their vision, or consider an off-label injection of bevacizumab at a drug cost of under $7 per injection. But, we didn't know if intravitreal bevacizumab would be safe or effective.

I approached the director of our pharmacy, Serafin Gonzalez, and asked him if he could compound bevacizumab into syringes for intravitreal injection. This type of request was nothing new for Serafin. He had been compounding drugs for off-label intravitreal use in ophthalmology for years, and these drugs included antibiotics, steroids, and another Genentech product known as tissue plasminogen activator. After reviewing federal guidelines and Chapter 797 of the US Pharmacopeia (USP), he said that it was legal and safe, as long as strict guidelines were followed.[28] My chairman, Carmen Puliafito, approved the compounding of bevacizumab for intravitreal injection and permitted my off-label use intravitreal bevacizumab as salvage therapy only in patients losing vision, only after they had failed routine clinical care—in other words, only after the approved therapies were tried. If I was to use the drug off-label, I realized that all patients needed to be informed of all the potential risks associated with bevacizumab, and because of our extensive experience with intravitreal ranibizumab and systemic bevacizumab, we were well positioned to know all the possible adverse events that could occur.

During the second week of May, almost 2 weeks after our fateful ARVO meeting, I identified the ideal exudative AMD patient for a bevacizumab injection. She was losing vision in her better-seeing eye owing to continued growth of her neovascular lesion after treatment with PDT followed by intravitreal pegaptanib. She was well aware of what was going to happen if we stayed the course, since she already had lost vision in her fellow eye from exudative AMD. Of note, the patient was a retired nurse and understood all the potential risks associated with an intravitreal injection of bevacizumab. For the first salvage dose of bevacizumab, I chose a 1.00 mg dose or 0.04 mL, and the patient was not charged for the drug or injection. After 1 injection of bevacizumab, the macular anatomy was restored and the vision was stabilized (Figures 9-11).[29] The OCT and visual acuity responses were nearly identical to the responses I had observed after intravitreal ranibizumab and systemic bevacizumab. An additional patient with macular edema from a central retinal vein occlusion was injected with 1.0 mg of bevacizumab, only this time the visual acuity improved when the macular edema resolved.[30] Both patients remained stable for 2 months after a single dose. No inflammation or any other adverse events were observed.

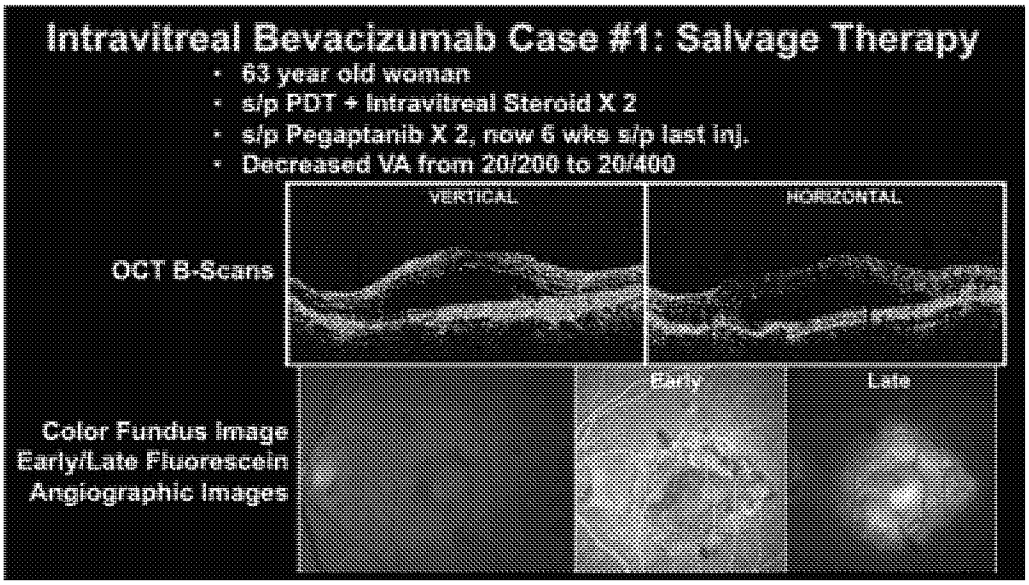


FIGURE 9. First case of salvage therapy with intravitreal bevacizumab following verteporfin photodynamic therapy (PDT) with intravitreal steroid and intravitreal pegaptanib sodium. Vertical and horizontal optical coherence tomography (OCT) B-scans show the presence of macular fluid and fluorescein angiography depicts a neovascular lesion associated with significant leakage. VA = visual acuity.

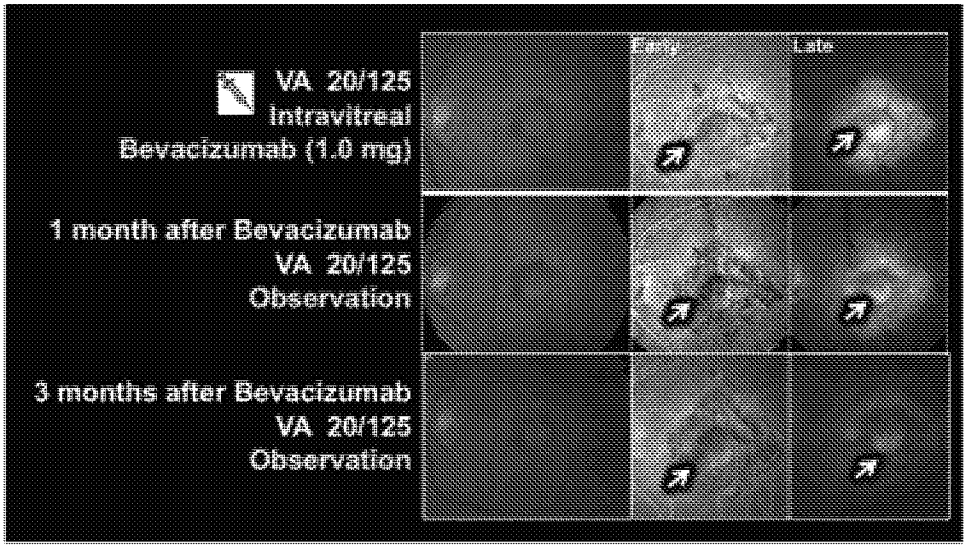


FIGURE 10. Fluorescein angiographic appearance following the intravitreal injection of bevacizumab (1.0 mg) into the eye shown in Figure 10 with a gradual decrease in leakage (arrow) from the neovascular lesion through 3 months of follow-up. VA = visual acuity.

THE GLOBAL BEVACIZUMAB REVOLUTION

IN MAY 2005, AFTER THE 2 PATIENTS WERE INJECTED WITH bevacizumab, my colleagues and I at the BPEI started to offer intravitreal bevacizumab as salvage therapy at no cost to patients. We treated exudative and neovascular eye diseases, such as exudative AMD, diabetic macular edema, and macular edema secondary to retinal vein occlusions. My plan was to keep our discovery quiet so we could design a controlled, prospective, randomized clinical trial to prove that intravitreal bevacizumab was safe and effective. However, news of our novel therapy started to spread outside of the institute, primarily driven by grateful patients. As inquiries from the outside increased, I realized we needed to get our initial observations published to

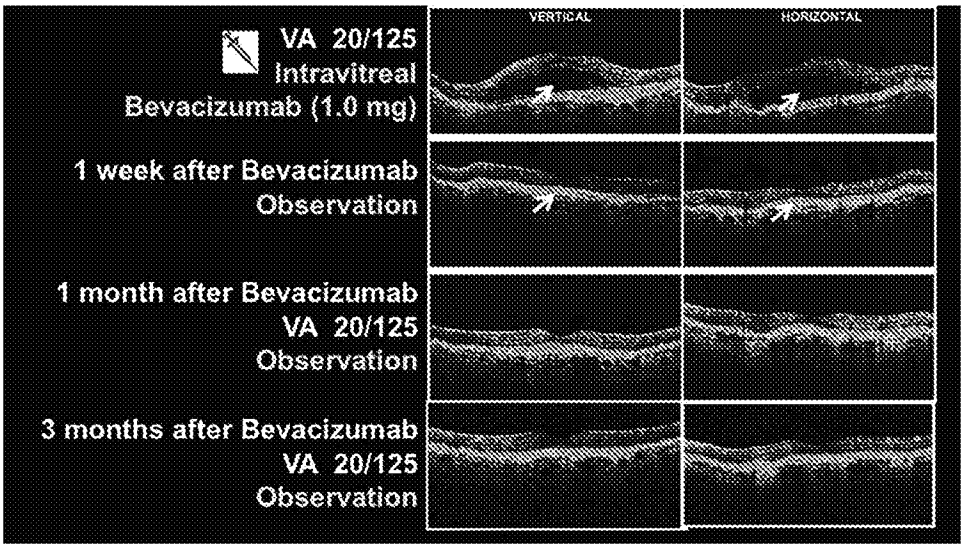


FIGURE 11. Vertical and horizontal optical coherence tomography B-scans of the eye shown in Figure 10 following the intravitreal injection of bevacizumab (1.0 mg) showing resolution of macular fluid by 1 week after the injection, which was maintained through 3 months. Overall, there was no objective improvement in vision, but the patient reported a significant subjective improvement. VA = visual acuity.

emphasize the use of bevacizumab as salvage therapy and the need for safe compounding of bevacizumab according to Chapter 797 guidelines from the USP. We were concerned, even at that time, that the irresponsible use of bevacizumab would result in endophthalmitis, a bacterial infection in the eye. For this reason, we reported both or original cases in the July issue of *Ophthalmic Surgery, Lasers, and Imaging*.[29,30] However, prior to the publication of these reports, our initial intravitreal bevacizumab results were shared with 2 respected colleagues, Robert Avery and Garee Thomas. Robert Avery learned of our bevacizumab experience at a June 2005 meeting in Montana, where my chairman, Carmen Puliafito, presented my first case of exudative AMD treated with intravitreal bevacizumab. Garee Thomas learned of our bevacizumab use during a casual conversation at a different meeting in June. After we shared our compounding and injection protocol with both of them, they started offering off-label intravitreal bevacizumab to their patients. Their early use of intravitreal bevacizumab would prove pivotal to the rapid adoption of intravitreal bevacizumab worldwide.

The world learned of our discovery at the American Society of Retina Specialists (ASRS) annual meeting in Montreal, which was held during the second week in July. The excitement surrounding this meeting was palpable because Genentech had planned to release the results from their phase 3 ranibizumab trial for minimally classic and occult neovascular AMD, known as the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trial. Even though I was the top enroller in that study and would be the first author on the *New England Journal of Medicine* 2-year report on this study,[31] Genentech asked Joan Miller to present the top-line results. I'm sure most of you can figure out why I wasn't offered the MARINA presentation, given the tensions that had developed between Genentech and me after they became fully aware of our bevacizumab discovery. However, it was the perfect sequence of events and couldn't have worked out better.

On July 18, 2005, there were 3 talks that would precede Joan Miller's talk on the MARINA results. I was scheduled to give the initial 12-week results from the SANA Study, Andrew Moshfeghi was scheduled to give the 24-week results, and Anne Fung was scheduled to give the 1-year results from the PrONTO Study. The meeting was packed with retina specialists, journalists, and investors. At the end of my talk on the SANA Study design and the short-term results using systemic bevacizumab, I showed the results from the first intravitreal injection of bevacizumab. We were able to demonstrate the similarity between an intravitreal injection of bevacizumab with an intravenous infusion of bevacizumab, and the intravitreal injection of ranibizumab, which was shown by Anne Fung in her PrONTO presentation. Then, after our presentations, Joan Miller presented the impressive MARINA ranibizumab results. It was the perfect storm. The crowd went wild. The OCT and visual acuity outcomes after the ranibizumab injections looked identical to the bevacizumab results. Moreover, this the first meeting where OCT imaging played an important, pivotal role in documenting the

anatomic changes that were associated with the vision improvement observed following anti-VEGF therapy. Everyone connected the dots. They concluded that if the OCT and visual acuity results looked similar and ranibizumab wasn't going to be available for a year, then the obvious solution was to use off-label bevacizumab now. Moreover, Robert Avery and Garee Thomas were in the audience telling everyone that their results looked as good as our results, and that intravitreal bevacizumab was the real deal and it was available now. The global bevacizumab revolution had started. Not only was bevacizumab available worldwide, but also, it was cheap, at about $7 a dose for the drug. Also, remember that retina specialists had become disillusioned with pegaptanib, and not only was bevacizumab less expensive than pegaptanib, it also appeared to be more effective.

After the intravitreal bevacizumab announcement at the ASRS meeting in Montreal, clinicians and researchers from all over the world started to work together to investigate its safety and efficacy.[32] Numerous groups initiated parallel animal studies and clinical studies. One of the most important collaborations was initiated between Anat Loewenstein's group in Tel Aviv and Robert Avery's group in Santa Barbara.[33] Using a rabbit model, they showed that bevacizumab was safe and that the intravitreal bevacizumab not only penetrated the retina, but persisted longer in the eye compared with ranibizumab. Over the following year, the clinical use of bevacizumab spread worldwide because of the global availability of bevacizumab, its low cost, its perceived safety and efficacy, and the enormous unmet need to prevent blindness. In the United States, Medicare providers from all over the country agreed to pay for the intravitreal use of bevacizumab for a wide range of ophthalmic indications. Our Medicare provider, First Coast, was the first to agree to pay for bevacizumab and over the next year, the other providers soon followed. This was accomplished owing to the hard work of our colleagues all over the country, particularly the AAO, and our specialty societies, with extraordinary assistance from William Rich and George Williams. As a result of this global enthusiasm, research publications describing intravitreal bevacizumab grew exponentially over the next few years.

In the midst of the global frenzy around intravitreal bevacizumab, I abandoned my plans to run a systemic bevacizumab study and decided to focus my efforts on a multicenter, prospective, randomized, sham-controlled study to investigate intravitreal bevacizumab in exudative AMD. We drafted a protocol known as the IntraVitreal Avastin in Neovascular AMD Study (IVANA Study) and submitted the IND application to the FDA. Wiley Chambers of the FDA was supportive of our efforts, but the application was placed on hold pending my responses to the following requests. They included (1) a detailed description of how the drug would be prepared by a licensed and accredited pharmacy and a description of how the drug would be handled once it was prepared; (2) a detailed description of the stability testing that would be performed to determine that bevacizumab was stable in syringes once dispensed by our pharmacy; (3) a revision of the protocol incorporating 2 different doses of bevacizumab at 1.25 mg (0.05 mL) and 2.5 mg (0.10 mL); and (4) a full retrospective review of all the patients treated with intravitreal bevacizumab at our site, with as much evidence as possible from other sites (including published papers and manuscripts submitted for publication) to help assess the number and kind of complications that might be expected. To comply with these requests, I submitted a retrospective research protocol to the University of Miami IRB to get permission to collect all the clinical information that had been recorded on our patients treated with off-label intravitreal bevacizumab. The university IRB requested that I submit an IND to the FDA for this retrospective review of off-label intravitreal bevacizumab. This request seemed extraordinarily unusual and should have given me advance warning that my use of off-label bevacizumab was starting to be of concern within the university. My retina colleagues and our patients were not generating this concern. But rather, individuals outside the university were voicing the concerns. Interestingly, there was no formal process to request an IND from the FDA for a retrospective review, but the university was undeterred from their demand that I receive FDA approval. As a result, I simply drew a box on the IND application form, labeled the box for a retrospective review, checked the box, and submitted the application. It was approved. Shortly thereafter, the university IRB approved the retrospective chart review and data collection commenced.

THE BAD AND THE UGLY BEHAVIOR OF INDUSTRY AND GOVERNMENT

I WAS IN THE PROCESS OF SATISFYING ALL THE FDA REquests, which included the IRB-approved retrospective review of all our patients treated with intravitreal bevacizumab, and the laboratory functional studies with cultured vascular endothelial cells to test the biological stability of bevacizumab by measuring its ability to inhibit cell growth in vitro after storage in syringes, when it all suddenly came to a screeching halt. On December 28, 2005, I received a fax from the Federal Office of Human Research Protection (OHRP) that contained a letter dated December 22, 2005. This 20-page, single-spaced letter with footnotes and 40 pages of accompanying exhibits alleged that I had committed research fraud and patient abuse by using bevacizumab. There was no doubt that this professionally written letter was the product of a law firm, but we were unable to determine who sent the letter, since its author was anonymized and all identifying information was redacted. The letter accused us of performing

egregious, dangerous, clandestine, and unauthorized human experimentation. The author included false reports of human injury and financial conflicts with bogus evidence that supposedly supported these claims. Eventually, these anonymous purveyors of fake information would lose, but I paid a price. I was intensively investigated by UM and the OHRP for 16 months. Every aspect of my bevacizumab use and all my research programs were extensively scrutinized. Finally, in April 2007, a panel of OHRP investigators, outside experts, and their lawyers came to the UM IRB office for a meeting with leadership and me. At this meeting I was totally exonerated and congratulated for my efforts to prevent blindness. Their conclusions were that my actions were legal, ethical, and appropriate for patient care. Although stressful, it was a valuable learning experience. If only my accusers had bothered to read the Belmont Report on the Ethical Principles and Guidelines for the Protection of Human Subjects of Research.[34] In that report, it is clearly written that in the United States, off-label drug use in the clinical care of patients is legal and not regulated by the FDA. To paraphrase the Belmont Report, just because the drug is used off-label, it doesn't make it research. The results of this investigation were posted online at the time, but the documents are no longer available on the OHRP website. Of course, my accusers weren't interested in the truth, but rather, they were interested in attacking me, damaging my credibility, and stopping the global use of bevacizumab. Needless to say, they failed. While I was distracted, my colleagues all over the world surged forward in their research and clinical use of intravitreal bevacizumab. Bevacizumab was a global juggernaut that could not be stopped, and to this day, I can only speculate who was behind this failed attempt to stop it. While I have no doubt that industry was behind the letter, I also believe they received a little help from an OHRP insider, although this can't be definitively proven. To this day, the identity of my accuser remains unknown.

While the OHRP exonerated me in April 2007, they weren't quite finished. In October 2007, I received an e-mail from the FDA stating that they would perform a surprise audit of all my clinical research studies under the jurisdiction of the FDA. Since I had received an IND from the FDA for my retrospective review of patients treated with intravitreal bevacizumab, they demanded an audit of all the medical records and data collection sheets pertaining to patients treated with intravitreal bevacizumab. When the auditor showed up from October 19th to the 21st, she embarrassingly shared the fact that the audit had been requested by OHRP and she had never before had to audit a retrospective review. However, as a professional, she took her assignment seriously and thoroughly reviewed every aspect of the medical records and data collection sheets pertaining to our patients with exudative AMD, diabetic macular edema, and retinal vein occlusions with macular edema treated with intravitreal bevacizumab. At the conclusion of the bevacizumab audit, we were totally vindicated. Bevacizumab had been administered as off-label salvage therapy and no prospective research was performed. Three retrospective review papers highlighting our off-label clinical use of intravitreal bevacizumab were subsequently published,[35–37] along with hundreds of papers from other researchers. The worldwide phenomenon of intravitreal bevacizumab could not be stopped.

THE GOOD AND THE GREAT BEHAVIOR OF SPECIALTY SOCIETIES AND GOVERNMENT

ANOTHER STRATEGY EMPLOYED BY INDUSTRY TO THWART the use of intravitreal bevacizumab was an attempt by Genentech to prevent the sale of bevacizumab to ophthalmologists. In mid-2007, Genentech announced that bevacizumab sales to ophthalmologists would be stopped, and the FDA demanded this action. To the credit of the AAO, the ASRS, the Macula Society, and the Retina Society, our leadership fought against this action using many different strategies, both public and clandestine. George Williams and Kirk Packo gave inspiring talks at the Retina Subspecialty Day in 2007 encouraging Genentech to change its decision. On November 7, 2007, at the annual meeting of the AAO, Susan Desmond-Hellman addressed a special session devoted to bevacizumab access. Susan Desmond-Hellman, then President for Product Development at Genentech who serves today as the Chief Executive Officer of the Bill and Melinda Gates Foundation, told an auditorium filled to capacity that the decision to restrict bevacizumab sales to ophthalmologists arose from FDA inspectors who found glass particles in lots of bevacizumab, determined that the bevacizumab was unsafe for intraocular use, mandated its destruction at a loss to Genentech of over $100 million, and required that sales of bevacizumab for intraocular use be restricted. Tense discussions followed, both during the annual meeting and afterwards. However, we soon found supporters within the government who understood the impact of restricting access to this low-cost drug. Although there were many heroes in the fight to preserve access to bevacizumab, one man stood out as a giant. His name is Jack Mitchell.

Jack Mitchell was Chief of Oversight and Investigation for the U.S. Senate Special Committee on Aging, which had broad jurisdiction over public health issues that affected seniors and the Center for Medicare and Medicaid Services (CMS), and this jurisdiction provided him with the opportunity to become involved and gain access to the information needed. At the time, Senator Herbert Kohl of Wisconsin was the ranking Democrat and chairman of the committee and Senator Robert Corker was the ranking Republican. Jack Mitchell investigated Genentech's bevacizumab policy and after reviewing all FDA audits and interviewing industry representatives, he

wrote an investigative report that was composed of 19 single-spaced pages (Supplemental Material, available at AJO.com). In this report, he highlighted the FDA's refusal to honor the request from Genentech that they change bevacizumab's labeling to explicitly state "not intended for ophthalmologic use." At the time, the FDA claimed that there were no safety-related issues to justify such a labeling change. Most likely, our FDA audit report and the numerous publications that had appeared in peer-reviewed journals served to support the FDA's position. Moreover, Jack Mitchell found that the FDA had identified manufacturing problems at Genentech's facility that resulted in glass particles in their product. The FDA inspection report highlighted deficient practices and the lack of effective processes at the facility and recommended that those lots be considered unfit for any use, oncology or ophthalmology. Of note, the FDA did not mandate the lot's destruction and did not recommend restricting the sale of bevacizumab to compounding pharmacies or restricting the intraocular use of bevacizumab. Owing to the diligence and perseverance of Jack Mitchell, our professional societies, and many other colleagues, Genentech backed down and permitted the sale of bevacizumab to compounding pharmacies for intraocular use.

While there were minor subsequent skirmishes in our attempts to get coverage from all Medicare providers across the United States, it wasn't until September 2009 that another major obstacle arose that threatened our use of intravitreal bevacizumab. Suddenly, CMS decided to stop paying for any intravitreal bevacizumab. No reason was given publicly. It appeared to be an arbitrary decision that was being implemented without due process. We had our suspicions why this happened, but no proof. Once again, our professional societies and our allies in Washington came to the rescue. Jack Mitchell played a pivotal role behind the scenes and started an investigation. Soon, another great advocate for bevacizumab surfaced and played a pivotal role within CMS. His name was Ross Brechner. He was a lead medical officer and consultant at CMS and the only ophthalmologist at CMS. Fortunately, we were able to get the CMS decision reversed.

Ross Brechner and I had become good friends by the time he helped reverse the CMS decision. Ross's professional career was a bit unusual in that he was a practicing ophthalmologist who went back later in life and obtained a master's degree in biostatistics and public health from the Johns Hopkins School of Public Health. He then went to work at the Centers for Disease Control and Prevention before moving on to CMS. In 2008, when he was at CMS, he became intrigued with the Medicare cost savings from the use of intravitreal bevacizumab compared with ranibizumab, which had been approved in 2006. We then started to collaborate on an investigation into the real-world use of ranibizumab and bevacizumab in 2008 based on the 100% of the Medicare database files. At that time, CMS was reimbursing about $2000 a dose for ranibizumab and $50 a dose for bevacizumab. As an employee of CMS, Ross had access to the 100% CMS databases from 2006 through 2008. We compiled the results and showed that in 2008, over 58% of exudative AMD patients had been treated with bevacizumab. With bevacizumab being reimbursed by CMS at $50 a dose and ranibizumab at $2000 a dose, we conservatively estimated that in 2008 alone, if all the bevacizumab doses had been replaced with ranibizumab doses, then CMS would have spent an additional $1 billion for the care of exudative AMD patients. We wrote a manuscript describing the number of intravitreal injections, the utilization of ranibizumab and bevacizumab, and the theoretical cost savings from bevacizumab, but Ross Brechner's boss at CMS, Barry Straube, refused to give us permission to submit our research for publication. We repeatedly approached Barry Straube for permission, but to no avail. Once again, Jack Mitchell came to the rescue. He introduced me to Alicia Mundy, a reporter at the *Wall Street Journal*, and I explained the situation to her. She investigated and wrote an article in the WSJ on June 17, 2010 entitled "Medicare Eye Study Finds Untapped Savings." In that article, Barry Straube denied any effort to hinder release of the data. He said he hadn't realized the authors viewed the matter as pressing and said, "I think we can speed this up significantly." Our paper was submitted soon after the WSJ article appeared, and Dr Straube left CMS shortly thereafter. Our research was published in the May 2011 issue of the *American Journal of Ophthalmology* (AJO).[38]

By the time the paper was published, we had already finished evaluating the 100% CMS database for 2009 and had begun evaluating the 2010 database. Ross Brechner had divided the United States by major metropolitan centers and rural areas, evaluated utilization of anti-VEGF therapy in these regions, determined the use of drugs based on the penetration of fee-for-service Medicare vs Medicare Advantage plans, and identified comorbidities associated with the use of the different drugs. Unfortunately, Ross Brechner died in August 2011 just as he was finalizing a draft of the 2009 CMS experience. All his data and the draft manuscript were on his computer, but CMS refused access to his computer, despite many attempts by Ross's colleagues at CMS to continue his research.

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY TO THE RESCUE!

TO CELEBRATE THE 25TH ANNIVERSARY OF CLINICAL OCT, the Association for Research in Vision and Ophthalmology (ARVO) sponsored a research project to investigate the financial return from the federal government's support for

basic science research to develop OCT. The strategy was to determine the return on investment from this original government research support. The financial return would be calculated based on how much money OCT-guided anti-VEGF therapy had saved CMS compared with the number of injections that would have been given if the drugs had been used according to the fixed-interval dosing for these anti-VEGF drugs on the FDA-approved labels. Using the 2008 data from the paper that Ross Brechner and I published based on the 100% Medicare fee-for-service database, the ARVO research team led by Mathew Windsor, of which I was a member, investigated additional 100% Medicare fee-for-service databases through 2015. The goal was to determine the number of unique patients with exudative AMD that had received injections of anti-VEGF drugs from 2009 through 2015, determine how many injections were actually given, and then estimate how many injections would have been given if each patient had followed a fixed-interval dosing regimen. By knowing the injection costs, the relative utilization of bevacizumab, ranibizumab, and aflibercept (Eylea; Regeneron, Tarrytown, New York, USA), and the cost of each drug, we were able to calculate the amount actually spent and estimate the amount that would have been spent using fixed-interval dosing. We then estimated the return on the government's funding for OCT research that had been provided through the National Science Foundation and the National Institutes of Health. We calculated the cost savings from OCT-guided therapy to be $11.2 billion for both patients and Medicare, with a savings of about $9 billion to Medicare alone. Based on basic science funding of approximately $400 million that was granted to develop OCT, the $9 billion cost savings to CMS represented at least a 21-fold return on investment. Since these data don't include the estimated 30% of Medicare recipients who are enrolled in Medicare Advantage plans, we could estimate that the overall return to Medicare and patients from the use of OCT-guided therapy was closer to $16 billion. This research was published in the January 2018 issue of the AJO.[39]

After this research project was completed, I asked ARVO if I could reanalyze the data and focus on the estimated cost savings from the use of bevacizumab between 2008 and 2015. We would accomplish this task by imagining a world in which bevacizumab had never been used to treat exudative AMD. If that were the case, then all the bevacizumab used between 2008 and 2015 would have been replaced by ranibizumab or aflibercept, depending on the proportion of each drug used in any given year. When we calculated the cost from using only FDA-approved drugs and compared that cost with the actual cost of patient care between 2008 and 2015 for patients with exudative AMD, we found that Medicare and patients saved $17.3 billion, and if we included the Medicare Advantage plans, the savings was closer to $24.7 billion.[40] Remember, my original systemic bevacizumab study (the SANA Study) was performed after raising $200 000 from grateful patients. Using the $200,000 as the basis for calculating a return on investment, we estimated that the use of intravitreal bevacizumab yielded a 123,500-fold return on investment. If we combine the overall cost savings from OCT-guided therapy ($16 billion) with the cost savings from bevacizumab ($24.7 billion), then we estimated a cost savings of $40.7 billion from treating exudative AMD alone. In the 2018 Patterns and Trends (PAT) survey from the ASRS, it is currently estimated that over 70% of clinicians use intravitreal bevacizumab as first-line therapy for the treatment of exudative AMD and the estimated use of bevacizumab from previous PAT surveys was in line with our estimates of its use in 2008 through 2015. Thus, if we include 2016 through 2018 in our cost-savings calculations and include the diagnoses of diabetic macular edema and macular edema from retinal vein occlusions from 2008 through 2018, it's probably safe to estimate a cost savings in excess of $50 billion from the use of OCT-guided therapy and the use of bevacizumab in the United States alone, and that doesn't even include the far greater worldwide savings from the use of bevacizumab and OCT-guided therapy.

THE GREAT AND THE GOOD PREVAILED OVER THE BAD AND THE UGLY

IN WRITING THIS JACKSON AWARD LECTURE, IT WAS IMPOSsible to mention all the marvelous clinicians, researchers, administrators, and government officials who contributed to the success of OCT-guided therapy and intravitreal bevacizumab for the treatment of exudative and neovascular ocular diseases. While New Retina Radio did an exceptional job capturing the history behind VEGF and the eye in a 3-part series based on the U.S. experience,[41] the story of bevacizumab and the eye is a global adventure full of scientific discovery and the tension between healthcare providers, industry, and government bureaucracies to maintain access to this low-cost therapy for blinding diseases. In particular, 2 research teams, led by Daniel Martin and Usha Chakravarthy, deserve acknowledgement for their significant contributions to this global narrative. As a result of their remarkable efforts in conducting the multicenter, prospective, randomized, controlled clinical trials known as the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Inhibit VEGF in Age-related choroidal Neovascularization (IVAN) trial,[42–45] they unequivocally demonstrated that both bevacizumab and OCT-guided therapy were safe and effective. While none of what we accomplished would have been possible without the industry-sponsored breakthroughs that have brought vision-saving therapies and imaging devices to our patients, it's also important to appreciate that as clinicians, we are obligated to do what's

right for our patients. When clinicians and industry work together as partners rather than adversaries, we can achieve greatness and improve the lives of our patients by preventing blindness and improving their vision.

FUNDING/SUPPORT: NO FUNDING OR GRANT SUPPORT. FINANCIAL DISCLOSURES: DR ROSENFELD HAS RECENTLY RECEIVED research support from Carl Zeiss Meditec, the Salah Foundation, the National Eye Institute Center Core Grant (P30EY014801), and Research to Prevent Blindness (unrestricted Grant) to the Department of Ophthalmology, University of Miami Miller School of Medicine. He is a consultant for Achillion Pharmaceuticals, Boehringer-Ingelheim, Carl Zeiss Meditec, Chengdu Kanghong Biotech, Ocunexus Therapeutics, Healios K.K., Hemera Biosciences, Isarna Pharmaceuticals, Lin Bioscience, NGM Biopharmaceuticals, Ocunexus, Ocudyne, Tyrogenex, and Unity Biotechnology. Dr Rosenfeld as has equity interest in Apellis, Verana Health, and Ocudyne. The author attests that he meets the current ICMJE criteria for authorship.

Other Acknowledgments: Dr Rosenfeld acknowledges the many contributors over the years, responsible for the success of clinical OCT imaging, the development of OCT-guided anti-VEGF therapies, and the successful introduction and widespread use of intravitreal bevacizumab for the treatment of neovascular and exudative ocular diseases.

REFERENCES

1. TAP Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. Treatment of age-related macular degeneration with photodynamic therapy. *Arch Ophthalmol* 1999;117(10):1329–1345.
2. TAP Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials- TAP Report 2. *Arch Ophthalmol* 2001;119(2):198–207.
3. Rosenfeld PJ, Feuer WJ. Lessons from recent Phase III trial failures: don't design Phase III trials based on retrospective subgroup analyses from Phase II trials. *Ophthalmology* 2018;125(10):1488–1491.
4. Rosenfeld PJ, Schwartz SD, Blumenkranz MS, et al. Maximum tolerated dose of a humanized anti-vascular endothelial growth factor antibody fragment for treating neovascular age-related macular degeneration. *Ophthalmology* 2005;112(6):1048–1053.
5. Heier JS, Antoszyk AN, Pavan PR, et al. Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. *Ophthalmology* 2006;113(4). 633.e1-e4.
6. Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N. Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Ophthalmology* 2006;113(4):623.e621.
7. Stewart MW, Rosenfeld PJ, Penha FM, et al. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor trap-eye). *Retina* 2012;32(3):434–457.
8. Fujimoto J, Swanson E. The development, commercialization, and impact of optical coherence tomography. *Invest Ophthalmol Vis Sci* 2016;57(9):OCT1–OCT13.
9. Rosenfeld PJ. Optical coherence tomography and the development of antiangiogenic therapies in neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2016;57(9):OCT14–26.
10. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol* 2007;143(4):566–583.
11. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol* 2009;148(1):43–58 e41.
12. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2013;120(5):1046–1056.
13. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2014;121(11):2181–2192.
14. Okada M, Kandasamy R, Chong EW, McGuinness M, Guymer RH. The treat-and-extend injection regimen versus alternate dosing strategies in age-related macular degeneration: a systematic review and meta-analysis. *Am J Ophthalmol* 2018;192:184–197.
15. Ng EW, Shima DT, Calias P, Cunningham ET Jr, Guyer DR, Adamis AP. Pegaptanib, a targeted anti-VEGF aptamer for ocular vascular disease. *Nat Rev Drug Discov* 2006;5(2):123–132.
16. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351(27):2805–2816.
17. Chakravarthy U, Adamis AP, Cunningham ET Jr, et al. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006;113(9). 1508.e1-25.
18. D'Amico DJ, Masonson HN, Patel M, et al. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006;113(6):992–1001.e1006.
19. Klettner A, Roider J. Comparison of bevacizumab, ranibizumab, and pegaptanib in vitro: efficiency and possible additional pathways. *Invest Ophthalmol Vis Sci* 2008;49(10):4523–4527.
20. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005;112(6):1035–1047.
21. Moshfeghi AA, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related

macular degeneration: twenty-four-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2006; 113(11). 2002.e1-12.
22. Chen Y, Wiesmann C, Fuh G, et al. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. *J Mol Biol* 1999;293(4):865–881.
23. Feinsod M, Chambers WA. Trials and tribulations: a primer on successfully navigating the waters of the Food and Drug Administration. *Ophthalmology* 2004;111(10):1801–1806.
24. Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. *Arch Ophthalmol* 1996;114(1):66–71.
25. Mordenti J, Cuthbertson RA, Ferrara N, et al. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. *Toxicol Pathol* 1999;27(5):536–544.
26. Bermingham-McDonogh O, McCabe KL, Reh TA. Effects of GGF/neuregulins on neuronal survival and neurite outgrowth correlate with erbB2/neu expression in developing rat retina. *Development* 1996;122(5):1427–1438.
27. Han DP. Intravitreal human immune globulin in a rabbit model of Staphylococcus aureus toxin-mediated endophthalmitis: a potential adjunct in the treatment of endophthalmitis. *Trans Am Ophthalmol Soc* 2004;102:305–320.
28. Gonzalez S, Rosenfeld PJ, Stewart MW, Brown J, Murphy SP. Avastin doesn't blind people, people blind people. *Am J Ophthalmol* 2012;153(2):196–203.e191.
29. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 2005;36(4): 331–335.
30. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for macular edema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging* 2005;36(4):336–339.
31. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1419–1431.
32. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006;90(11): 1344–1349.
33. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina* 2006;26(3):262–269.
34. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Available at: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html. Accessed June 16, 2019.
35. Rich RM, Rosenfeld PJ, Puliafito CA, et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina* 2006;26(5): 495–511.
36. Gregori NZ, Gaitan J, Rosenfeld PJ, et al. Long-term safety and efficacy of intravitreal bevacizumab (Avastin) for the management of central retinal vein occlusion. *Retina* 2008; 28(9):1325–1337.
37. Gregori NZ, Rattan GH, Rosenfeld PJ, et al. Safety and efficacy of intravitreal bevacizumab (avastin) for the management of branch and hemiretinal vein occlusion. *Retina* 2009;29(7):913–925.
38. Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 Medicare fee-for-service part B claims file. *Am J Ophthalmol* 2011;151(5):887–895.e881.
39. Windsor MA, Sun SJJ, Prick KD, Swanson EA, Rosenfeld PJ, Huang D. Estimating public and patient savings from basic research - a study of optical coherence tomography in managing antiangiogenic therapy. *Am J Ophthalmol* 2018;185: 115–122.
40. Rosenfeld PJ, Windsor MA, Feuer WJ, et al. Estimating Medicare and patient savings from the use of bevacizumab for the treatment of exudative age-related macular degeneration. *Am J Ophthalmol* 2018;191:135–139.
41. New Retina Radio. 2018. Available at: https://eyetube.net/podcasts/new-retina-radio/. Accessed February 23, 2019.
42. Comparison of Age-related Macular Degeneration Treatments Trials Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364(20): 1897–1908.
43. Comparison of Age-related Macular Degeneration Treatments Trials Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119(7):1388–1398.
44. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN Randomized Trial. *Ophthalmology* 2012;119(7):1399–1411.
45. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet* 2013;382(9900):1258–1267.

Complementary and Coordinated Roles of the VEGFs and Angiopoietins during Normal and Pathologic Vascular Formation

N.W. GALE, G. THURSTON, S. DAVIS, S.J. WIEGAND, J. HOLASH, J.S. RUDGE, AND G.D. YANCOPOULOS
Regeneron Pharmaceuticals, Inc., Tarrytown, New York 10591

Mammalian organisms depend on their vasculature to deliver nutrients and oxygen to all of their tissues, to transport products (such as hormones and antibodies) from certain cells to distant parts of the body, and to carry away waste products. The development of a functioning vasculature, as well as its proper integration into the tissues it serves, depends on myriad interactions and communications between the many cell types involved. Although a large number of signals are involved in mediating these intercellular communications, a great deal of focus has been directed to growth factors that are members of either the vascular endothelial growth factor (VEGF) family or the angiopoietin family. Why the focus on these two families of growth factors? First of all, these two families of growth factors are unique in that they act via receptors that are largely restricted to the vasculature endothelium—this very restricted distribution of their receptors indicates that these two families of growth factors evolved to play very particular roles specifically involving the vasculature. Moreover, genetic approaches—involving gene knockouts and transgenic overexpression in mice—have spectacularly confirmed the very critical and very specific roles played by members of these two growth factor families during vascular development. Thus, the focus on the VEGFs and angiopoietins seems well-placed based on their action via vascular-specific receptors and the confirmation of their critical and specific vascular roles based on genetic studies in mice. Since the VEGFs have been extensively dealt with in a number of excellent reviews (Eriksson and Alitalo 1999; Ferrara 1999; Yancopoulos et al. 2000; Carmeliet et al. 2001), this review highlights work from our laboratory regarding the angiopoietins, although much of this work is presented in the context of the complementary and reciprocal actions of the angiopoietins as compared to the VEGFs.

MOLECULAR CLONING OF THE Tie RECEPTORS AND THEIR ANGIOPOIETIN LIGANDS

Although the VEGFs utilize a number of accessory receptor components such as the neuropilins, the primary actions of the VEGFs appear to be mediated via three closely related receptor tyrosine kinases, now referred to as VEGF receptor 1 (VEGFR-1, previously known as Flt-1), VEGF receptor 2 (VEGFR-2, previously known as KDR or Flk-1), and VEGF receptor 3 (VEGFR-3, previously known as Flt-3) (Eriksson and Alitalo 1999; Ferrara 1999; Yancopoulos et al. 2000; Carmeliet et al. 2001). The various VEGFs have an overlapping set of specificities for the three VEGF receptors (Fig. 1A). These VEGF receptors are conventional members of the receptor tyrosine kinase superfamily, which also includes as members the receptors for the epidermal growth factors (EGFs), the fibroblast growth factors (FGFs), the platelet-derived growth factors (PDGFs), and many other key growth factors. The critical distinguishing feature of the VEGF receptors is their cellular distribution. That is, the VEGF receptors are unlike the other aforementioned growth factor

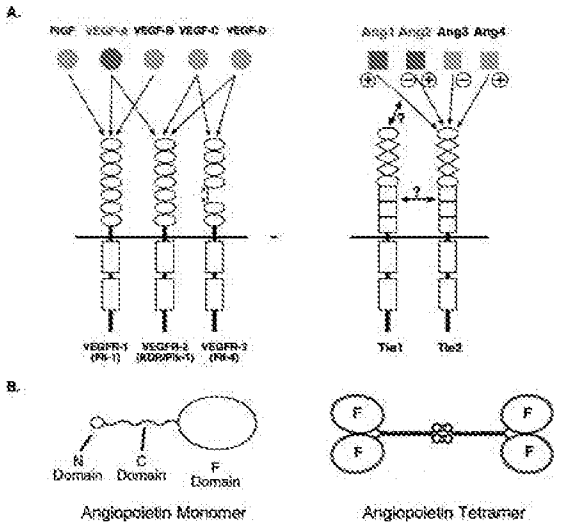


Figure 1. (*A*) Schematic summary of interactions of VEGFs with their receptors, and of angiopoietins with their Tie receptors. (*B*) On left, schematic view of angiopoietin monomer indicating amino-terminal domain (N domain), coil-coil domain (C domain), and fibrinogen-like domain (F domain). The F domain is the receptor-binding portion of this complex ligand, whereas the C domain serves to dimerize two F domains, and the N domain acts to further multimerize these dimers into tetramers, as shown on the right, or even higher-order structures (not shown).

receptors in that they are largely restricted to the vascular endothelium, both during development and in the adult. This very restricted distribution of their receptors indicates that the VEGFs evolved to play unique roles that very specifically involve the vasculature.

Because of an appreciation of how specifically important the VEGFs are for vascular development, and the realization that this specificity directly resulted from the restricted distribution of their receptors to the vasculature, we and other workers searched for additional families of receptor tyrosine kinases that might, like the VEGF receptors, be largely restricted to the vasculature. These efforts led to the discovery of a novel two-member family of receptor tyrosine kinases, now known as the Ties, that were indeed as restricted to the vasculature as were the VEGF receptors (Korhonen et al. 1992; Dumont et al. 1993; Iwama et al. 1993; Maisonpierre et al. 1993; Sato et al. 1993). At the time of their discovery, the Tie1 and Tie2 receptors were referred to as "orphans," since their binding partners had not yet been identified. However, it was presumed that the unidentified binding partners for these receptors would be growth factors specific for the vasculature.

To identify their presumably very interesting ligands, we converted the Tie receptor ectodomains into detection reagents that we used to identify sources of potential ligands, and then we used a novel expression cloning strategy (termed Secretory Trap expression cloning) in order to molecularly clone the first ligand for the Ties, which we termed angiopoietin-1 (Davis et al. 1996). We then cloned additional angiopoietins based on their homology with angiopoietin-1 (Maisonpierre et al. 1997; Valenzuela et al. 1999). All of the known angiopoietins bind primarily to the same Tie receptor, Tie2, and it is unclear whether there are independent ligands for the second Tie receptor, Tie1, or (as currently seems more likely) whether the known angiopoietins can in some way or under some circumstances also engage Tie1, perhaps as a second component in a heteromerized complex (Fig. 1A). Interestingly, whereas angiopoietin-1 is an obligate activator of its Tie2 receptor, angiopoietin-2 seems to be a more complex regulator of this receptor; that is, under some conditions it seems to activate Tie2, whereas under other conditions it may act as a blocker of this receptor (Maisonpierre et al. 1997).

UNIQUE MODULAR STRUCTURE OF THE ANGIOPOIETINS: BINDING AND MULTIMERIZATION MOTIFS

The angiopoietins have a modular structure unlike that of any previously characterized growth factor (Davis et al. 2003). This modular structure consists of a receptor-binding domain, a dimerization motif, and a supercluster-ing motif that forms variable-sized multimers (Fig. 1B). Genetic engineering of precise multimers of the receptor-binding domain of angiopoietin-1, using surrogate multimerization motifs, reveals that tetramers (Fig. 1B) are minimally required for activating endothelial Tie2 receptors, whereas engineered dimers can antagonize endothelial Tie2 receptors (Davis et al. 2003). Surprisingly, angiopoietin-2 has a modular structure and multimerization state similar to that of angiopoietin-1, and its dual agonist/antagonist activities appear to be encoded in its receptor-binding domain (Davis et al. 2003).

INSIGHTS FROM KNOCKOUTS AND TRANSGENICS OF ANGIOPOIETIN-1: ROLES IN VESSEL MATURATION, STABILIZING THE VESSEL WALL, AND REGULATING VESSEL SIZE

The most important insights into the normal roles of angiopoietin-1 and its Tie2 receptor came from the analysis of mice engineered to lack these gene products (Dumont et al. 1994; Sato et al. 1995; Suri et al. 1996). Unlike mouse embryos lacking VEGF or VEGFR-2, embryos lacking angiopoietin-1 or Tie2 develop a rather normal primary vasculature. However, this vasculature fails to undergo normal further remodeling. The most prominent defects are in the heart, with problems in the associations between the endocardium and underlying myocardium, as well as in trabecula formation, and also in the remodeling of many vascular beds into large and small vessels. In these vascular beds, as in the heart, ultrastructural analysis suggests that endothelial cells fail to associate appropriately with underlying support cells, which are the cells that provide the angiopoietin-1 protein that acts on endothelial Tie2 receptors (Suri et al. 1996). This finding has led to the suggestion that angiopoietin-1 via Tie2 does not supply an instructive signal that actually directs specific vascular remodeling events, but rather plays more of a permissive role by optimizing the manner in which endothelial cells integrate with supporting cells, thus allowing the cells to receive other critical signals from their environment (Suri et al. 1996). Altogether, insights from the analysis of mice lacking angiopoietin-1 led to the suggestion that it played a key role, complementary to that of VEGF, to allow vessel maturation and vessel wall stabilization (Fig. 2).

Transgenic overexpression of angiopoietin-1 in the skin resulted in a dramatic hypervascularization phenotype (Suri et al. 1998; Thurston et al. 1999). Although there are modest increases in vessel number, the most dramatic increase is in vessel size. In contrast, VEGF in similar models primarily increases vessel number. These findings suggest that angiopoietin-1 may promote circumferential vessel growth as opposed to sproutive growth. Combining transgenic overexpression of angiopoietin-1 and VEGF leads to unprecedented increases in vascularity, which result from a combination of increases in both vessel size and number (Thurston et al. 1999). The vascular patterns induced by the combination are still obviously abnormal in morphology, suggesting that much must be learned about exploiting even this growth factor combination in therapeutic settings so as to grow normal vessels.

Recent insights based on delivery of angiopoietin-1 protein to newborn and adult mice confirm that it has very different vascular growth effects than does VEGF (G. Thurston et al., in prep.). Whereas VEGF primarily promotes angiogenic sprouting, angiopoietin-1 primarily

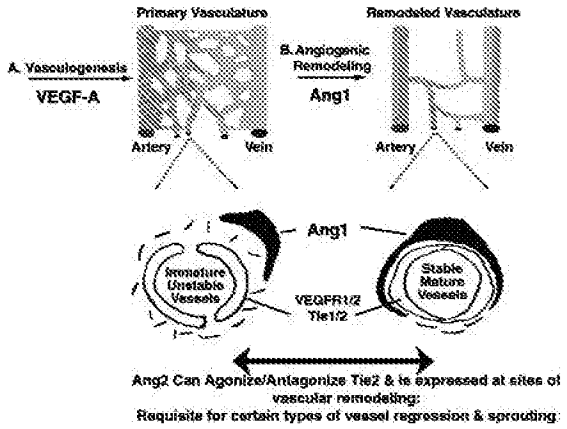


Figure 2. Schematic summary of the complementary and coordinated roles of the VEGFs and angiopoietins during vascular development. VEGF-A acts initially to form the primitive primary vasculature, angiopoietin-1 acts to mature and stabilize this primitive vasculature, in part by optimizing interactions between endothelial cells and their surrounding support cells. Angiopoietin-2 is expressed, and acts, at sites of subsequent remodeling of a previously stable vasculature and is requisite for certain types of vascular regressions and sprouting.

promotes circumferential vessel enlargement in the complete absence of angiogenic sprouting. Interestingly, these effects of angiopoietin-1 seem to be regulated in a stage- and segment-specific manner. That is, angiopoietin-1 can primarily promote circumferential enlargement of "plastic" and "immature" vessels, as opposed to mature vessels. Moreover, it promotes enlargement of venous vessels but not arterial vessels.

ANGIOPOIETIN-1 CAN ALSO OPPOSE VASCULAR PERMEABILITY ACTIONS OF VEGF

In addition to their disparate effects on vascular morphology, transgenic overexpression of angiopoietin-1 and VEGF also leads to dramatically distinct effects on vascular function and integrity. Transgenic VEGF produces immature, leaky, inflamed, and hemorrhagic vessels (Detmar et al. 1998; Larcher et al. 1998; Thurston et al. 1999). On the other hand, transgenic angiopietin-1 results in vessels that are actually resistant to leak, whether the leak is induced by VEGF or by inflammatory agents (Thurston et al. 1999). This resistance appears related to the ability of angiopoietin-1 to maximize interactions between endothelial cells and their surrounding support cells and matrix, as the angiopoietin-1 vessels are resistant to treatments that normally create holes in the endothelial cell barrier (Thurston et al. 1999). These findings suggested that angiopoietin-1 might act counter to VEGF as an anti-permeability factor, and raised an assortment of therapeutic possibilities (Thurston et al. 1999). There are numerous disease processes—ranging from diabetic retinopathy to inflammation to brain edema following ischemic stroke—in which vessels become damaged and leaky, and an agent that was able to repair the damage and prevent the leak could have enormous therapeutic benefit. To be considered for such applications, angiopoietin-1 would have to exhibit its anti-leak actions not only when applied transgenically during vessel development, but also when acutely administered to the adult animal. Furthermore, angiopoietin-1 would not only have to be able to protect against leak acutely, but also to accomplish this without causing acute changes in vascular morphology. Supporting the clinical potential of angiopoietin-1 in settings of vascular leak, acute adenoviral administration of angiopoietin-1 to adult animals demonstrated that angiopoietin-1 could indeed acutely protect the adult vasculature from vascular leak, without inducing immediate changes in vascular morphology (Thurston et al. 2000).

ANGIOPOIETIN-2: COMPLEX REGULATOR OF Tie2 WITH DIVERSE ROLES IN POSTNATAL VASCULAR REMODELING

Angiopoietin-2 was cloned on the basis of its homology with angiopoietin-1, and it displayed similarly high affinity for the Tie2 receptor (Maisonpierre et al. 1997). Angiopoietin-2 differed from angiopoietin-1 in that, depending on the cell examined, angiopoietin-2 could either activate or antagonize the Tie2 receptor on cultured cells (Maisonpierre et al. 1997). Initial insights into the function of angiopoietin-2 came from the realization that it was dramatically induced in the endothelium of vessels undergoing active remodeling, such as sprouting or regressing vessels in the ovary (Maisonpierre et al. 1997; Goede et al. 1998), or in tumors (Stratmann et al. 1998; Holash et al. 1999a,b; Zagzag et al. 1999). These findings, together with the possibility that angiopoietin-2 could act as a dual Tie2 agonist/antagonist, led to the hypothesis (Fig. 2) that angiopoietin-2 might play a key (but complex) role at sites of angiogenic remodeling (Maisonpierre et al. 1997; Holash et al. 1999a,b; Zagzag et al. 1999). This possibility was recently confirmed by analysis of mice knocked out for angiopoietin-2 (Gale et al. 2002). This analysis revealed that angiopoietin-2, unlike VEGF and angiopoietin-1, is not requisite during embryonic vascular development, but instead is necessary during subsequent postnatal vascular remodeling. Specifically, postnatal vascular remodeling was explored in the neonatal eye, one of the most thoroughly studied sites of postnatal vascular remodeling (Alon et al. 1995; Stone et al. 1995, 1996; Benjamin et al. 1998; Ito and Yoshioka 1999; Hackett et al. 2000). During eye development, an initial vasculature, known as the hyaloid vasculature, is formed which nourishes the lens, while the retina is initially avascular. In the rodent, in the first few weeks after birth, the initial hyaloid vasculature regresses, while sprouts from the central artery of the eye produce a retinal vasculature; these simultaneous vascular regression and sprouting phenomena are thought to be coupled in some manner. In mice lacking angiopoietin-2, the initial eye vasculature at birth appears normal (i.e., the hyaloid vasculature), indicating that angiopoietin-2 is dispensable for formation of the initial vasculature (Gale et al. 2002). However, the mice fail to undergo normal remodeling of the eye vasculature in the first two postnatal weeks; that

is, their hyaloid vasculature does not regress, nor does sprouting from the central artery occur to form the retinal vasculature (Gale et al. 2002). Moreover, in these mice, the angiopoietin-2 gene was replaced by a reporter gene (β-galactosidase), allowing high-resolution detection of sites of angiopoietin-2 expression (Gale et al. 2002). This reporter gene approach revealed that angiopoietin-2 was indeed highly expressed precisely at the sites of vascular remodeling—within the hyaloid vessels during regression, as well as at the site of sprouting from the central artery.

Altogether, these data confirm that angiopoietin-2 plays a critical and requisite role at sites of vascular remodeling, both during vessel regression and during vessel sprouting. Thus, our studies reveal that angiopoietin-2 is the first angiogenic factor genetically confirmed to be dispensable for embryonic angiogenesis but specifically required for normal postnatal vascular remodeling. It remains unclear as to whether angiopoietin-2 is acting as an agonist or antagonist of the Tie2 receptor during these processes. In addition, subsequent studies have revealed that certain types of pathological angiogenesis can proceed in the angiopoietin-2 knockouts, indicating that although it is required for some normal forms of vascular remodeling and angiogenesis, it may not be required for all.

ANGIOPOIETIN-2: UNEXPECTED REQUISITE ROLE DURING LYMPHATIC VESSEL DEVELOPMENT

As noted above, prior observations that angiopoietin-2 was expressed at sites of vascular remodeling presaged the finding in the mouse knockouts that this factor was required for certain types of postnatal vascular remodeling. There were no such prior clues to suggest that angiopoietin-2 might also play a crucial role during lymphatic vessel development. This was a completely unexpected finding that resulted from an obvious abnormality noted in the mice lacking angiopoietin-2 (Gale et al. 2002). These knockout mice, shortly after feeding, developed engorged abdomens filled with milky fluid. Subsequent analyses revealed that this corresponded to profound chylous ascites due to malfunctioning lymphatic lacteals in the intestines. Moreover, the mice developed widespread lymphatic dysfunction, characterized by widespread tissue edema and correlating with morphologically abnormal lymphatics at every site examined. Thus, genetic deletion of angiopoietin-2 results in profound and widespread defects in the patterning and function of the lymphatic vasculature (Gale et al. 2002).

To learn more about the mechanism of action of angiopoietin-2, we generated mice in which the angiopoietin-2 gene was replaced with cDNA encoding angiopoietin-1 (Gale et al. 2002). Surprisingly, angiopoietin-1 completely rescued the lymphatic defects in mice lacking angiopoietin-2, indicating that angiopoietin-2 acts as a Tie2 agonist in the lymphatic vasculature.

Because some of the vascular defects seen in mice lacking angiopoietin-1 have been attributed to disrupted interactions between the vascular endothelium and supporting smooth muscle cells, we examined the lymphatics in the angiopoietin-2 knockout mice for their smooth muscle investiture. Indeed, whereas the well-defined lymphatic channels seen in control pups were closely enveloped by smooth muscle cells, the disorganized lymphatic networks found in angiopoietin-2 knockout mice were often surrounded by poorly associated clusters of smooth muscle cells. These findings are consistent with a model in which local angiopoietin-2 expression, provided by the lymphatics themselves and/or by adjacent large blood vessels, acts on Tie2 receptors within the lymphatics in a manner that is necessary for proper lymphatic development. On the basis of the gene rescue studies in which the angiopoietin-2 coding region is replaced with that of angiopoietin-1, it appears that angiopoietin-2 is acting as an agonist of Tie2 during lymphatic development, perhaps by promoting interactions between lymphatic endothelium and smooth muscle, just as angiopoietin-1 seems to do for the blood vessel development.

Previous studies demonstrated that members of the VEGF family, most likely both VEGF-C and VEGF-D working via VEGFR-3, play critical roles in the development of the lymphatic vasculature (Kukk et al. 1996; Jeltsch et al. 1997; Karkkainen et al. 2000; Makinen et al. 2001; Veikkola et al. 2001). Just as earlier work revealed that members of the VEGF and angiopoietin families (i.e., VEGF-A and angiopoietin-1) are obligate partners during the development of blood vasculature (Dumont et al. 1994; Sato et al. 1995; Suri et al. 1996), our current findings suggest that VEGF-C and VEGF-D also obligately require angiopoietin-2 in order to form functional lymphatics (Fig. 3). As appears to be the case for the blood vasculature, the angiopoietins are not required for the initiation of lymphatic vascular development, unlike other key lymphatic regulators such as the transcription factor Prox-1 (Wigle and Oliver 1999) or the VEGF-C/VEGFR-3 pathway (Kukk et al. 1996; Jeltsch et al. 1997; Karkkainen et al. 2000; Makinen et al. 2001; Veikkola et al. 2001). Rather, angiopoietin-2 seems to play a key role in subsequent remodeling and maturation of the lymphatics, in a manner that is absolutely required for their normal function, as suggested for angiopoietin-1 within the blood vasculature (Fig. 3). Because angiopoietin-1 is able to rescue the lymphatic defect, angiopoietin-2 appears to be acting as an activating agonist in this situation. As has also been proposed for angiopoietin-1 and the blood vasculature, the role of angiopoietin-2 in

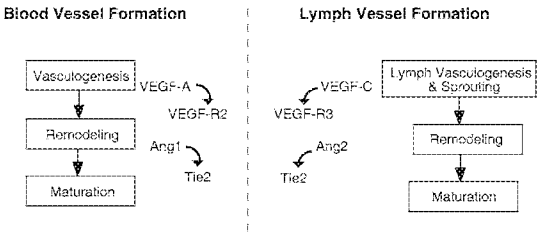


Figure 3. Schematic indicating that just as VEGF-A and angiopoietin-1 collaborate during formation of the blood vasculature, VEGF-C/D and angiopoietin-2 act together in analogous ways during formation of the lymphatic vasculature.

the lymphatic vasculature may well involve the optimizing of interactions between endothelial cells and surrounding smooth muscle cells. Thus, our studies demonstrate that members of the VEGF and angiopoietin families work together not only during development of the blood vasculature, but also during development of the lymphatic vasculature.

ROLES OF ANGIOPOIETINS AND VEGFs IN TUMOR ANGIOGENESIS: EFFICACY OF VEGF TRAP IN TUMOR MODELS

Previous studies had found that angiopoietin-2, as well as the Tie receptors, is dramatically induced within the endothelium during tumor angiogenesis (Stratmann et al. 1998; Holash et al. 1999a,b; Zagzag et al. 1999). This led to the proposal that the angiopoietin/Tie system might be as useful a target for tumor angiogenesis as the VEGF system. More recent studies have not validated the utility of this system for tumor angiogenesis, and we have not been able to demonstrate dramatic effects of promoting or blocking Tie receptor function during tumor angiogenesis. Similarly, tumors can grow in mice lacking angiopoietin-2, although there may be subtle alterations in the resulting tumor vessels. All this has left us with the conclusion that the VEGF pathway remains the best validated target pathway for approaches aimed at controlling tumor growth by blocking required tumor angiogenesis. To take advantage of this realization, we developed a very potent VEGF blocker termed the VEGF trap (Holash et al. 2002). Recent application of this agent indicates that it may be very useful in the treatment of angiogenesis-dependent tumors (Holash et al. 2002; Kim et al. 2002), as well as in other settings in which VEGF and associated vascular leak or angiogenesis may be causing clinical problems, such as in diabetic retinopathy, age-related macular edema, endometriosis, and tumor-associated ascites and effusions.

CONCLUSIONS

Our findings reveal that the angiopoietins are important modulators of blood and lymphatic vessel formation and function, working in a collaborative and cooperative manner with members of the VEGF family. For the blood vasculature, angiopoietin-1 seems to work subsequent to VEGF-A so as to promote vessel maturation and vessel wall function. Interestingly, angiopoietin-1 seems to act reciprocally as compared to VEGF-A with regard to vascular leak—with VEGF-A promoting leak and permeability, and angiopoietin-1 seemingly opposing these actions. Similarly, in terms of the regulation of vascular growth, VEGF-A and angiopoietin-1 also appear to act quite differently, with VEGF-A promoting angiogenic sprouting and angiopoietin-1 instead regulating circumferential vessel size.

In terms of the blood vasculature, angiopoietin-2 is unlike VEGF-A and angiopoietin-1 in that it is dispensable for normal embryonic vascular development, since mice lacking angiopoietin-2 are born and appear quite normal initially. However, as predicted by observations that angiopoietin-2 is highly induced at sites of vascular remodeling, this factor is indeed required for certain types of postnatal vascular remodelings, such as the normal regressions and sprouting seen in the eye after birth. Surprisingly, however, angiopoietin-2 may not be absolutely required for all types of postnatal angiogenesis, consistent with observations that the angiopoietin/Tie system may not be as critical for tumor angiogenesis as the VEGF system.

Just as VEGF-A and angiopoietin-1 seem to collaborate during initial formation of the blood vasculature, it appears as if VEGF-C/D and angiopoietin-2 collaborate in similar manner during formation of the lymphatic vasculature. Many of the features of this collaboration in the lymphatic vasculature are reminiscent of those that characterize the collaboration in the blood vasculature. That is, the VEGF family members seemingly play key initiating roles in both blood and lymphatic vessel formation, whereas the angiopoietin family members seem to play subsequent maturation roles, potentially involving the optimization of endothelial–smooth muscle cell interactions. It is perhaps not surprising that nature seems to have duplicated the players and roles it uses to produce these two different types of vasculatures.

On the basis of our work with the VEGFs and the angiopoietins, it becomes clear that there are a large number of critical growth factors involved in the physiological regulation of blood vessel formation, and the actions of these molecular players must be very carefully orchestrated in terms of time, space, and dose so as to form a functioning vascular network. The complexity of the process makes ongoing therapeutic efforts aimed at growing new vascular networks to treat ischemic disease appear quite challenging. For example, delivery of just VEGF, or even delivery of an imbalance of VEGF compared to angiopoietin-1, has the potential to cause more harm (by forming malfunctioning vessels prone to leak and hemorrhage) than good. The same sorts of complexities must now be considered in attempts to therapeutically promote lymphatic vessel growth so as to treat certain edematous conditions. It appears as if there is more to learn about how various combinations of factors interact during vessel formation in order to exploit these factors for the therapeutic growth of vessels, whether it be blood vessels in settings of ischemia, or lymphatic vessels in settings of lymphedema.

Although the complexities of vascular formation create major challenges for those trying to therapeutically grow vessels, these same complexities may work in favor of therapeutic approaches aimed at blocking vessel growth (so as to benefit diseases ranging from cancer to endometriosis, or neovascularization conditions of the eye such as occur in settings of diabetic retinopathy or age-related macular degeneration). That is, blockade of many different molecular players may all result in the blunting of vessel formation. There is no doubt that VEGF is the best-validated target for antiangiogenesis therapies, based on overwhelming genetic, mechanistic, and animal efficacy data.

Recent efforts also suggest heretofore unimagined applications for vascular growth factors. For example, the

possibility that angiopoietin-1 may help prevent or repair damaged and leaky vessels offers therapeutic hope for an assortment of unmet clinical needs, such as in the vascular leak which creates major problems in diabetic retinopathy, acute macular degeneration, ischemia/reperfusion injury as occurs following strokes and ARDS, or in inflammatory settings. The continued discovery and characterization of the molecular players regulating vessel formation are sure to lead to additional unexpected therapeutic opportunities, as well as to the refinement of current therapeutic approaches aimed at growing or blocking vessel formation.

REFERENCES

Alon T., Hemo I., Itin A., Pe'er J., Stone J., and Keshet E. 1995. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. *Nat. Med.* **1:** 1024.

Benjamin L.E., Hemo I., and Keshet E. 1998. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. *Development* **125:** 1591.

Carmeliet P., Moons L., Luttun A., Vincenti V., Compernolle V., De Mol M., Wu Y., Bono F., Devy L., Beck H., Scholz D., Acker T., DiPalma T., Dewerchin M., Noel A., Stalmans I., Barra A., Blacher S., Vandendriessche T., Ponten A., Eriksson U., Plate K.H., Foidart J.M., Schaper W., Charnock-Jones D.S., Hicklin D.J., Herbert J.M., Collen D., and Persico M.G. 2001. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. *Nat. Med.* **7:** 575.

Davis S., Aldrich T.H., Jones P.F., Acheson A., Compton D., Vivek J., Ryan T., Bruno J., Radjiewski C., Maisonpierre P.C., and Yancopoulos G.D. 1996. Isolation of angiopoietin-1, a ligand for the TIE2 receptor, by secretion-trap expression cloning. *Cell* **87:** 1161.

Davis S., Papadopoulos N., Aldrich T.H., Maisonpierre P.C., Huang T., Kovac L., Xu A., Leidich R., Radziejewska E., Goldberg J., Jain V., Bailey K., Karow M., Fandl J., Samuelsson S.J., Ioffe E., Rudge J.S., Daly T.J., Radziejewski C., and Yancopoulos G.D. 2003. Angiopoietins as modular growth factors with distinct functionally essential domains for receptor binding, dimerization, and superclustering. *Nat. Struct. Biol.* **10:** 38.

Detmar M., Brown L.F., Schon M.P., Elicker B.M., Velasco P., Richard L., Fukumura D., Monsky W., Claffey K.P., and Jain R.K. 1998. Increased microvascular density and enhanced leukocyte rolling and adhesion in the skin of VEGF transgenic mice. *J. Invest. Dermatol.* **111:** 1.

Dumont D.J., Gradwohl G.J., Fong G.-H., Auerbach R., and Breitman M.L. 1993. The endothelial-specific receptor tyrosine kinase, *tek*, is a member of a new subfamily of receptors. *Oncogene* **8:** 1293.

Dumont D.J., Gradwohl G., Fong G.-H., Puri M.C., Gerstenstein M., Auerbach A., and Breitman M.L. 1994. Dominant-negative and targeted null mutations in the endothelial receptor tyrosine kinase, tek, reveal a critical role in vasculogenesis of the embryo. *Genes Dev.* **8:** 1897.

Eriksson U. and Alitalo K. 1999. Structure, expression and receptor-binding properties of novel vascular endothelial growth factors. *Curr. Top. Microbiol. Immunol.* **237:** 41.

Ferrara N. 1999. Vascular endothelial growth factor: Molecular and biological aspects. *Curr. Top. Microbiol. Immunol.* **237:** 1.

Gale N.W., Thurston G., Hackett S.F., Renard R., Wang Q., McClain J., Martin C., Witte C., Witte M.H., Jackson D., Suri C., Campochiaro P.A., Wiegand S.J., and Yancopoulos G.D. 2002. Angiopoietin-2 is required for postnatal angiogenesis and lymphatic patterning, and only the latter role is rescued by angiopoietin-1. *Dev. Cell* **3:** 411.

Goede V., Schmidt T., Kimmina S., Kozian D., and Augustin H.G. 1998. Analysis of blood vessel maturation processes during cyclic ovarian angiogenesis. *Lab. Invest.* **78:** 1385.

Hackett S.F., Ozaki H., Strauss R.W., Wahlin K., Suri C., Maisonpierre P., Yancopoulos G., and Campochiaro P.A. 2000. Angiopoietin 2 expression in the retina: Upregulation during physiologic and pathologic neovascularization. *J. Cell. Physiol.* **184:** 275.

Holash J., Wiegand S.J., and Yancopoulos G.D. 1999a. New model of tumor angiogenesis: Dynamic balance between vessel regression and growth mediated by angiopoietins and VEGF. *Oncogene* **18:** 5356.

Holash J., Maisonpierre P.C., Compton D., Boland P., Alexander C.R., Zagzag D., Yancopoulos G.D., and Wiegand S.J. 1999b. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science* **284:** 1994.

Holash J., Davis S., Papadopoulos N., Croll S.D., Ho L., Russell M., Boland P., Leidich R., Hylton D., Burova E., Ioffe E., Huang T., Radziejewski C., Bailey K., Fandl J.P., Daly T., Wiegand S.J., Yancopoulos G.D., and Rudge J.S. 2002. VEGF-Trap: A VEGF blocker with potent antitumor effects. *Proc. Natl. Acad. Sci.* **99:** 11393.

Ito M. and Yoshioka M. 1999. Regression of the hyaloid vessels and pupillary membrane of the mouse. *Anat. Embryol.* **200:** 403.

Iwama A., Hamaguchi I., Hashiyama M., Murayama Y., Yasunaga K., and Suda T. 1993. Molecular cloning and characterization of mouse *Tie* and *Tek* receptor tyrosine kinase genes and their expression in hematopoietic stem cells. *Biochem. Biophys. Res. Commun.* **195:** 301.

Jeltsch M., Kaipainen A., Joukov V., Meng X., Lakso M., Rauvala H., Swartz M., Fukumura D., Jain R.K., and Alitalo K. 1997. Hyperplasia of lymphatic vessels in VEGF-C transgenic mice. *Science* **276:** 1423.

Karkkainen M.J., Ferrell R.E., Lawrence E.C., Kimak M.A., Levinson K.L., McTigue M.A., Alitalo K., and Finegold D.N. 2000. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat. Genet.* **25:** 153.

Kim E.S., Serur A., Huang J., Manley C.A., McCrudden K.W., Frischer J.S., Soffer S.Z., Ring L., New T., Zabisky S., Rudge J.S., Holash J., Yancopoulos G.D., Kandel J.J., and Yamashiro D.J. 2002. Potent VEGF blockade causes regression of coopted vessels in a model of neuroblastoma. *Proc. Natl. Acad. Sci.* **99:** 11399.

Korhonen J., Partanen J., Armstrong E., Vaahtokari A., Elenius K., Jalkanen M., and Alitalo K. 1992. Enhanced expression of the *tie* receptor tyrosine kinase in endothelial cells during neovascularization. *Blood* **80:** 2548.

Kukk E., Lymboussaki A., Taira S., Kaipainen A., Jeltsch M., Joukov V., and Alitalo K. 1996. VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development. *Development* **122:** 3829.

Larcher F., Murillas R., Bolontrade M., Conti C.J., and Jorcano J.L. 1998. VEGF/VPF overexpression in skin of transgenic mice induces angiogenesis, vascular hyperpermeability and accelerated tumor development. *Oncogene* **17:** 303.

Maisonpierre P.C., Goldfarb M., Yancopoulos G.D., and Gao G. 1993. Distinct rat genes with related profiles of expression define a TIE receptor tyrosine kinase family. *Oncogene* **8:** 1631.

Maisonpierre P.C., Suri C., Jones P.F., Bartunkova S., Wiegand S.J., Radziejewski C., Compton D., McClain J., Aldrich T.H., Papadopoulos N., Daly T.J., Davis S., Sato T.N., and Yancopoulos G.D. 1997. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis (comments). *Science* **277:** 55.

Makinen T., Jussila L., Veikkola T., Karpanen T., Kettunen M.I., Pulkkanen K.J., Kauppinen R., Jackson D.G., Kubo H., Nishikawa S., Yla-Herttuala S., and Alitalo K. 2001. Inhibition of lymphangiogenesis with resulting lymphedema in transgenic mice expressing soluble VEGF receptor-3. *Nat. Med.* **7:** 199.

Sato T.N., Qin Y., Kozak C.A., and Audus K.L. 1993. *tie-1* and

tie-2 define another class of putative receptor tyrosine kinase genes expressed in early embryonic vascular system. *Proc. Natl. Acad. Sci.* **90:** 9355.

Sato T.N., Tozawa Y., Deutsch U., Wolburg-Buchholz K., Fujiwara Y., Gendron-Maguire M., Gridley T., Wolburg H., Risau W., and Qin Y. 1995. Distinct roles of the receptor tyrosine kinases Tie-1 and Tie-2 in blood vessel formation. *Nature* **376:** 70.

Stone J., Chan-Ling T., Pe'er J., Itin A., Gnessin H., and Keshet E. 1996. Roles of vascular endothelial growth factor and astrocyte degeneration in the genesis of retinopathy of prematurity. *Invest. Ophthalmol. Vis. Sci.* **37:** 290.

Stone J., Itin A., Alon T., Pe'er J., Gnessin H., Chan-Ling T., and Keshet E. 1995. Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. *J. Neurosci.* **15:** 4738.

Stratmann A., Risau W., and Plate K.H. 1998. Cell type-specific expression of angiopoietin-1 and angiopoietin-2 suggests a role in glioblastoma angiogenesis. *Am. J. Pathol.* **153:** 1459.

Suri C., McLain J., Thurston G., McDonald D.M., Oldmixon E.H., Sato T.N., and Yancopoulos G.D. 1998. Angiopoietin-1 promotes increased vascularization in vivo. *Science* **282:** 468.

Suri C., Jones P.F., Patan S., Bartunkova S., Maisonpierre P.C., Davis S., Sato T.N., and Yancopoulos G.D. 1996. Requisite role of angiopoietin-1, a ligand for the Tie2 receptor, during embryonic angiogenesis. *Cell* **87:** 1171.

Thurston G., Suri C., Smith K., McClain J., Sato T.N., Yancopoulos G.D., and McDonald D.M. 1999. Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. *Science* **286:** 2511.

Thurston G., Rudge J.S., Ioffe E., Zhou H., Ross L., Croll S.D., Glazer N., Holash J., McDonald D.M., and Yancopoulos G.D. 2000. Angiopoietin-1 protects the adult vasculature against plasma leakage. *Nat. Med.* **6:** 460.

Valenzuela D., Griffiths J., Rojas J., Aldrich T.H., Jones P.F., Zhou H., McClain J., Copeland N.G., Gilbert D.J., Jenkins N.A., Huanh T., Papadopoulos N., Maisonpierre P.C., Davis S., and Yancopoulos G.D. 1999. Angiopoietins 3 and 4: Diverging gene counterparts in mouse and man. *Proc. Natl. Acad. Sci.* **96:** 1904.

Veikkola T., Jussila L., Makinen T., Karpanen T., Jeltsch M., Petrova T.V., Kubo H., Thurston G., McDonald D.M., Achen M.G., Stacker S.A., and Alitalo K. 2001. Signalling via vascular endothelial growth factor receptor-3 is sufficient for lymphangiogenesis in transgenic mice. *EMBO J.* **20:** 1223.

Wigle J.T. and Oliver G. 1999. Prox1 function is required for the development of the murine lymphatic system. *Cell* **98:** 769.

Yancopoulos G.D., Davis S., Gale N.W., Rudge J.S., Wiegand S.W., and Holash J. 2000. Vascular-specific growth factors and blood vessel formation. *Nature* **407:** 242.

Zagzag D., Hooper A., Friedlander D.R., Chan W., Holash J., Wiegand S.J., Yancopoulos G.D., and Grumet M. 1999. In situ expression of angiopoietins in astrocytomas identifies angiopoietin-2 as an early marker of tumor angiogenesis. *Exp. Neurol.* **159:** 391.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/055,847	08/06/2018	George D. Yancopoulos	REGN-008CIPCON3	3451

96387 7590 12/10/2019

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
12/10/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

Office Action Summary	Application No. 16/055,847	Applicant(s) Yancopoulos, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 06 August 2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21-23 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21-23 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The preliminary amendment filed 06 August 2018 has been entered in full. Claims 1-20 have been cancelled, and claims 21-23 have been added. Therefore, claims 21-23 are pending and the subject of this Office action.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 06 August 2018, 19 June 2019, and 18 September 2019 have been considered by the examiner.

4. The Third Party Submission under 37 CFR 1.290 has been considered by the Examiner.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim(s) 21 and 23 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety

in Central Retinal Vein Occlusion (CRVO); published 13 November 2009; hereinafter Clinical Trial).

7. The Clinical Trial discloses methods for treating macular edema following as a consequence of retinal vein occlusion in a human subject (See pg. 1), the method comprising administering 2 mg aflibercept to the subject by intravitreal injection once every 4 weeks (See pg. 2). While the Clinical Trial reference does not explicitly state that the aflibercept was in a pharmaceutical composition comprising a pharmaceutically acceptable carrier, the protein being administered by intravitreal injection would inherently include a pharmaceutical composition comprising a pharmaceutically acceptable carrier. Thus, the Clinical Trial reference meets all the limitations of claims 21 and 23.

Claim Rejections - 35 USC § 103

8. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

11. Claim 22 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO); published 13 November 2009; hereinafter Clinical Trial) as applied to claims 21 and 23 above, and further in view of Gutierrez et al. (Clinical Ophthalmology. 2(4):787-791; published 2008).

12. The teachings of the Clinical Trial reference are summarized above. The Clinical Trial reference does not disclose wherein the aflibercept is administered in a volume of 0.05 ml.

13. However, such injection volumes for intravitreal injection were known in the art at the time the invention was made, as disclosed by Gutierrez et al. For example, Gutierrez et al disclose methods of macular edema secondary to retinal vein occlusion by the intravitreal injection of bevacizumab in a volume of 0.05 ml (See pg. 788).

14. It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the injection volume taught by Gutierrez et al in the treatment method as

disclosed by the Clinical Trial reference, as both methods utilize intravitreal injections in the treatment of macular edema secondary to retinal vein occlusion.

15. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Summary

16. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON M LOCKARD/
Examiner, Art Unit 1647
December 5, 2019

Notice of References Cited	Application/Control No. 16/055,847	Applicant(s)/Patent Under Reexamination Yancopoulos, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Gutierrez et al. (2008). Clin. Ophthalmol. 2(4):787-791.
	V	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO). 2009. 7 pages.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/055,847	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		12/05/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	12/05/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	12/05/2019	JML
PALM: Inventor search.	12/05/2019	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

1	Lucentis Label title ,7 pages, 30/06/2010	☐	☒
2	Peter AUTHER, Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator title, 9 pages , 30/08/2008	☐	☒

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

Signature	/Elizabeth Thompson/		
Name/Print	Elizabeth	Registration Number (if applicable)	

Examiner Signature	/JON M LOCKARD/	Date Considered	12/03/2019

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7303746	2007-12-04	Wiegand	
	2	7303748	2007-12-04	Wiegand	
	3	7306799	2007-12-11	Wiegand	
	4	9254338	2016-02-09	Yancopoulos	
	5	9669069	2017-06-06	Yancopoulos	
	6	10130681	2018-11-20	Yancopoulos	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2006/047325	2006-03-04	Genentech, Inc.		
	2	WO 2012/097019	2012-07-19	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	BROWNING et al. "Aflibercept for age-related macular degeneration: a game-changer or quiet addition?" American Journal of Ophthalmology, Vol. 154(2):222-226 (08/01/2012)	
	2	CAMPOCHIARO et al. "Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator" 16(4):791-799 (2008)	
	3	CAO, "A Subretinal Matrigel Rat Choroidal Neovascularization (CNV) Model and Inhibition of CNV and Associated Inflammation and Fibrosis by VEGF Trap" Investigative Ophthalmology & Visual Science, 51(11):6009- 6017 (11/2010)	
	4	EICHTEN, "Rapid decrease in tumor perfusion following VEGF blockade predicts long-term tumor growth inhibition in preclinical tumor models" Angiogenesis, 16:429-441 (2013)	
	5	HO, "VEGF Trap-Eye in Wet AMD - CLEAR-IT 2: One-Year OCT and FA Outcomes" CLEAR-IT 2 Study Group, pp 1-24 (09/28/2008)	
	6	HOLASH, "VEGF-Trap: A VEGF blocker with potent antitumor effects" PNAS 99(17)11393-11398 (8/20/2002)	
	7	HOLASH, "Inhibitors of growth factor receptors, signaling pathways and angiogenesis as therapeutic molecular agents." Cancer Metastasis 25:243-252 (2006)	
	8	KUO, "Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer" PNAS 98(8):4605-4610 (04/10/2001)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	OHR, "Aflibercept in wet age-related macular degeneration: a perspective review" Ther. Adv. Chronic Dis., 3(4):153-161 (2012)	
	10	PAPADPPOULOS, "Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab" Angiogenesis, 15:171-185 (2012)	
	11	Regeneron Press Release "Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)" September 14, 2009	
	12	REGILLO et al., "Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: OIER Study Year 1" American Journal of Ophthalmology, 145(2):239-248 (2008)	
	13	SCHNICHELS, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." Br. J. Opthalmol. (05/17/2013)	
	14	SHARMA and S. AND KAISER, P. K., Update on VEGF TRAP-Eye Clinical Trials and Retinal. Physician, 2010, Nov/Dec, p.1-6, <URL: https://www.retinalphysician.com/issues/2010/nov-dec/update-on-vegf-trap-eye-clinical-trials>	
	15	STEWART et al., "Predicted biological activity of intravitreal VEGF Trap" British Journal of Ophthalmology, 2008, vol.92, no.5, p.667-668	
	16	STEWART, "Aflibercept" Nature Reviews: Drug Discovery 11:269-270 (04/01/2012)	
	17	THURSTON, "Vascular endothelial growth factor and other signaling pathways in developmental and pathologic angiogenesis." International Journal of Hematology 80:7-20 (2004)	
	18	WACHSBERGER, "VEGF trap in combination with radiotherapy improves tumor control in u87 glioblastoma." Int. J. Radiation Oncology Biol Phys. 67(5):1526-1537 (2007)	
	19	ADSIS R&D Profile "Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye." Drugs R D, 9(4):261-269 (2008)	
	20	N/A "Materials from June 2011 FDA Committee Mtg" (06/17/2011)	
	21	N/A "Materials from Dec 2011 FDA Committee Mtg"(12/01/2011)	

Examiner Signature	/JON M LOCKARD/	Date Considered	11/25/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

EAST Search History

/J.L./

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	7722	(flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:36
L2	1959	l1 and ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:36
L3	808	l1 same ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:36
L4	7538	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:36
L5	414	l4 with ((chimer$ or fusion) with vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:36
L6	616	(l4 or l5) and (macular adj edema)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:37
L7	25	(l3 or l5) same (macular adj edema)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:38
L8	465	yancopoulos-g$.in.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:38
L9	0	l7 and l8	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:38
L10	9	l6 and l8	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:38
L11	9	l10 and (macular adj edema).clm.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/12/05 17:38

12/ 5/ 2019 5:40:10 PM
C:\ Users\ jlockard\ Documents\ EAST\ Workspaces\ 16055847.wsp

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 3451

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/055,847	08/06/2018 RULE	424	1647	REGN-008CIPCON3

APPLICANTS

Regeneron Pharmaceuticals, Inc., Tarrytown, NY

INVENTORS

George D. Yancopoulos, Yorktown Heights, NY;

**** CONTINUING DATA ***************************

This application is a CON of 15/471,506 03/28/2017 PAT 10130681
which is a CON of 14/972,560 12/17/2015 PAT 9669069
which is a CON of 13/940,370 07/12/2013 PAT 9254338
which is a CIP of PCT/US2012/020855 01/11/2012
which claims benefit of 61/432,245 01/13/2011
and claims benefit of 61/434,836 01/21/2011
and claims benefit of 61/561,957 11/21/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

08/21/2018

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JON MCCLELLAND LOCKARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	1	3	1

ADDRESS

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

TITLE

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	☐ All Fees
1720	No._____ to charge/credit DEPOSIT ACCOUNT	☐ 1.16 Fees (Filing)
	No._____ for following:	☐ 1.17 Fees (Processing Ext. of time)
		☐ 1.18 Fees (Issue)
		☐ Other _____
		☐ Credit

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

1	RAFAEL Author, Advances in the Medical Treatment of Diabetic Retinopathy, 7 pages, 08/31/2009, DIABETES CARE publisher	☐	☒
2	Niral Karia Author, Retinal vein occlusion: pathophysiology and treatment options title, 8 pages, 07/31/2010, Clinical Ophthalmology publisher	☐	☒
3	Vascular Endothelial Growth Factor Trap‐Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US	☐	☒

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16055847

☐	The fee set forth in 37 CFR 1.290(f) has been submitted herewith.
☒	The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.
☐	This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

Signature	/Joe Reynolds/		
Name/Print	Joe	Registration Number (if applicable)	

Examiner Signature	/JON M LOCKARD/	Date Considered	12/03/2019

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

ClinicalTrials.gov Identifier: NCT01012973

Recruitment Status : Completed
First Posted : November 13, 2009
Results First Posted : November 22, 2012
Last Update Posted : November 3, 2014

Sponsor:
Bayer

Collaborator:
Regeneron Pharmaceuticals

Information provided by (Responsible Party):
Bayer

Study Details | Tabular View | Study Results | Disclaimer

How to Read a Study Record

Study Description

Go to

Brief Summary:

To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion

Condition or disease	Intervention/treatment	Phase
Retinal Vein Occlusion	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Other: Sham treatment	Phase 3

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	177 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Study Start Date :	October 2009
Actual Primary Completion Date :	February 2011
Actual Study Completion Date :	February 2012

Resource links provided by the National Library of Medicine

NIH NLM

MedlinePlus related topics: Edema

Drug Information available for: Aflibercept Ziv-aflibercept

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Other: Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.	Other: Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Outcome Measures

Go to

Primary Outcome Measures :

1. Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures [Time Frame: Baseline and Week 24]

Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.

Secondary Outcome Measures :

1. Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) [Time Frame: Baseline and Week 24]

   Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.

2. Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF [Time Frame: Baseline and Week 24]
3. Percentage of Participants Who Developed Neovascularization During the First 24 Weeks [Time Frame: From baseline until Week 24]

   Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24

4. Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF [Time Frame: Baseline and Week 24]

   The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight

5. Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF [Time Frame: Baseline and Week 24]

EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).

Eligibility Criteria

Go to

Information from the National Library of Medicine NIH NLM

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts and Locations

Go to

Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT01012973***

Show 73 Study Locations

Sponsors and Collaborators

Bayer

Regeneron Pharmaceuticals

Investigators

Study Director: Bayer Study Director Bayer

More Information

Go to

Additional Information:

Click here to find results for studies related to Bayer Healthcare products. Click here to find information about studies related to Bayer Healthcare products conducted in Europe

Publications of Results:

Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, Vitti R, Berliner AJ, Hiemeyer F, Beckmann K, Zeitz O, Sandbrink R. VEGF Trap-Eye for macular oedema

secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013 Mar;97(3):278-84. doi: 10.1136/bjophthalmol-2012-301504. Epub 2013 Jan 7. Erratum in: Br J Ophthalmol. 2015 Dec;99(12):1746.

Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, Honda M, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202-208. doi: 10.1016/j.ophtha.2013.08.012. Epub 2013 Sep 29.

Responsible Party:	Bayer
ClinicalTrials.gov Identifier:	NCT01012973 History of Changes
Other Study ID Numbers:	14130
	2009-010973-19 (EudraCT Number)
First Posted:	November 13, 2009 Key Record Dates
Results First Posted:	November 22, 2012
Last Update Posted:	November 3, 2014
Last Verified:	October 2014

Keywords provided by Bayer:

- Macular Edema
- Central Retinal Vein Occlusion
- CRVO
- VEGF Trap-Eye
- best-corrected visual acuity

Additional relevant MeSH terms:

- Retinal Vein Occlusion
- Retinal Diseases
- Eye Diseases
- Venous Thrombosis
- Thrombosis
- Embolism and Thrombosis
- Vascular Diseases
- Cardiovascular Diseases

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	To Be Assigned
				Filing Date	August 6, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A 1647
				Examiner Name	N/A Jon Lockard
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7396664	2008-07-08	Daly et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	20050163798	2005-07-28	Papadopoulos et al.	
	2	20050260203	2005-11-24	Wiegand et al.	
	3	20060058234	2006-03-16	Daly et al.	
	4	20060172944	2006-08-03	Wiegand et al.	
	5	20070190058	2007-08-16	Shams	
	6	20030171320	2003-09-11	Guyer	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2000/75319	2000-12-14	Regeneron Pharmaceuitcals, Inc.		
	2	WO 2007/022101 A2	2007-02-22	Regeneron Pharmaceuticals, Inc.		
	3	WO 2008/063932	2008-05-29	Genentech, Inc.		
	4	JP 2010-509369	2010-03-25	Genentech, Inc.	See WO 2008/063932 for English Equivalent	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (June 2006)	
	2	Information from ClinicalTrials.gov archive View of NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" *ClinicalTrials.gov*. Web. 2010-11-30.	
	3	CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 21-756 MEDICAL REVIEW(S) (December 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>	
	4	CENTER FOR DRUG EVALUATION AND RESEARCH BLA APPLICATION NUMBER: 125156 MEDICAL REVIEW, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000_Lucentis_MedR.pdf>	
	5	CHARLES, Steve (Guest Lecturer) "VEGF Trap Has Positive DME Data" Tenth Annual Retina Fellows Forum Jan 29 and 30, Chicago, Article Date 03/01/2010	

Examiner Signature	/JON M LOCKARD/	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	To Be Assigned
				Filing Date	August 6, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	2	of	3	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	6	DIXON et al., "VEGF Trap-Eye for the treatment of neobascular age-related macular degeneration" Expert Opin. Investig. Drugs (2009) 18 (10): 1-8.	
	7	DO et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema" Br J Opthamol. 93(2):144-1449 (February 2009)	
	8	DO et al., "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema" Opthamology 118(9):1819-1826 (September 2011)	
	9	THE EYETECH STUDY GROUP, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration" American Academy of Ophthamology, 110(5):979-986 (May 2003)	
	10	HEIERet al., " rhuFab V2 (anti-VEGF Antibody) for Treatment of Exudative AMD" Symposium 8:Experimental and Emerging Treatments for Choroidal Neovascularization, 10 pp (2002)	
	11	HEIER et al., "RhuFab V2 in Wet AMD - 6 Month Continued Improvement Following Multiple Intravitreal Injections" Invest Ophthalmol Vis Sci, 44:E-Abstract 972 (2003)	
	12	HEIER et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012)	
	13	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" version available and updated on 17 March 2008.	
	14	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (12-01-2009)	
	15	Information from ClinicalTrials.gov archive on the view of NCT00789477 "DME and VEGF Trap-Eye: Investigation of Clinical Impact" (11-18-2010)	
	16	Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (01-07-2011)	
	17	KRZYSTOLIK et al., "Prevention of Experimental Choroidal NEovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment" Arch Ophthamol., 120:338-346 (Mar. 2002)	
	18	MITRA et al., "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions" Expert Review in Ophthalmo, Taylor & Francis, GB (January 1, 2011) 6(6):623-629	
	19	MOUSA AND MOUSA, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration" Biodrugs 2010; 24(3); 183-194.	
	20	NGUYEN et al., "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" Opthamology, J.B. Lippincott Co., Philadelphia, PA, US, 116(11):2141-2148 (November 1, 2009) 116(11):2141-2148 (November 1, 2009)	
	21	NGUYEN et al., "A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration" Ophthalmology (Sept 2006) 113(9):1522e1-1522e14 (epub July 28,2006)	

Examiner Signature	/JON M LOCKARD/	Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	To Be Assigned
				Filing Date	August 6, 2018
				First Named Inventor	YANCOPOULOS, GEORGE D.
				Art Unit	N/A
				Examiner Name	N/A
Sheet	3	of	3	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	22	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 20013)	
	23	OLIVERA et al., "VEGF Trap R1R2 suppresses experimental corneal angiogenesis" European Journal of Ophthalmology (January 1, 2010) 20(1):48-54	
	24	PAI et al., "Current concepts in intravitreal drug therapy for diabetic retinopathy" Saudi Journal of Opthamology 24(4):143-149 (June 30, 2010)	
	25	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007	
	26	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.	
	27	Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" November 22, 2010	
	28	Regeneron Press Release "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)" December 20, 2010	
	29	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (September 28, 2008) (XP-002770952)	
	30	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, Volume 32, Number 8, August 2009	
	31	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008.	
	32	STEWART, "THe expanding role of vascular endothelial growth factor inhibitors in opthamology" Mayo Clin Proc. 87(1):77-88 (January 2012)	
	33	THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 28, 2008)	
	34	WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)" Vol. 20, No. 2, 2006, pages 115-119.	

Examiner Signature	/JON M LOCKARD/	Date Considered	11/25/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Inventor Information for 16/055847

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Grz

Search Another: Application # Search **or Patent #** Search **or International Registration #** Search

PCT / / Search **or PG PUBS #** Search

Attorney Docket # Search

Bar Code # Search

To Go BACK Use BACK Button on Your BROWSER Tool Bar
Back to PALM | ASSIGNMENT | OASIS | Home page

Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to retinal vein occlusion

Juan Carlos Mesa Gutiérrez
Luis Arias Barquet
Josep Maria Caminal Mitjana
Sergi Prades Almolda
Nùria Planas Domènech
Octavi Pujol Goita
Marc Rubio Caso
Jorge Arruga Ginebreda

Department of Ophthalmology, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

Objective: To evaluate efficacy and safety of intravitreal injections of bevacizumab in the treatment of macular edema secondary to retinal vein occlusion (RVO).

Methods: Prospective study, noncomparative, interventional case series. Twelve consecutive patients (12 eyes) with macular edema associated with nonischemic retinal vein occlusion were treated with intravitreal bevacizumab (1.25 mg). All subjects underwent standardized ophthalmic evaluation at baseline and at weeks 1, 4, 12, and 24, consisting of visual acuity (VA) measurement using ETDRS charts, and imaging with ocular coherence tomography evaluating changes in foveal thickness (FT) and macular volume (MV).

Results: The median age was 66 years (± 4.16), and the median duration of symptoms was 4 months (± 1.81). There were six cases of inferior branch vein occlusion and six cases of superior branch retinal vein occlusion. Mean VA improved from 1.32 ± 0.24 (logMAR values) at baseline to 0.8 ± 0.15 ($p = 0.0003$) at the 6-month follow-up. The macular edema responded promptly, and a trend to restoration of normal macular anatomy was observed at by the seventh day. Mean FT improved from 615.50 ± 116.29 microns to 420 ± 72.53 microns ($p = 0.001$), and the mean MV improved from 19.81 ± 2.31mm3 to 9.23 ± 1.38 ($p = 0.0001$) at the 6-month follow-up.

Keywords: Bevacizumab, retinal vein occlusion, intravitreal injection, vascular endothelial growth factor

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease, after diabetic retinopathy. Visual loss may result from ischemic damage and/or macular edema. Early treatment may be required to improve vision because longstanding macular edema results in irreversible photoreceptor damage (CRVO 1995). Intravitreal triamcinolone is a treatment option that has demonstrated promising short-term results for the management of macular edema associated with RVO (Mohammed et al 2007). A multicenter, randomized and controlled clinical trial (Standard Care Versus Corticosteroid for Retina Vein Occlusion Study) is currently underway.

Retinal vein occlusion is associated with varying amounts of retinal ischaemia and, consequently, increased concentrations of vascular endothelial growth factor (VEGF) (Hayreh 1983). Early case reports on bevacizumab showed an increase in visual acuity (VA) and a decrease in macular edema secondary to exudative age-related macular degeneration (AMD) and central retinal vein occlusion (CRVO) (Rosenfeld et al 2005a). A nonrandomized study of intravitreal bevacizumab in patients with CRVO resulted in reduced macular swelling and increased VA (Iturralde et al 2006). However, because a physiological level of vascular endothelial growth factor may be necessary to maintain the homeostasis of the retina, care might be required to avoid the possible negative consequences of a complete blockade of VEGF.

Correspondence: Juan Carlos Mesa Gutiérrez
Department of Ophthalmology, Hospital Universitari de Bellvitge. Feixa Llarga s/n 08907. L'Hospitalet de Llobregat, Barcelona, Spain
Tel +34 93 260 7705
Fax +34 93 260 7981
Email juancarlosmesa@lycos.co.uk

These reports, along with results from preclinical and human studies that suggest a possible role of VEGF in RVO and the absence of a proven therapy, prompted us to investigate the effects of intravitreal bevacizumab injection in patients with macular edema associated with RVO.

Methods

Study design

This was a prospective, consecutive, noncomparative study that adhered to the Declaration of Helsinki and which was approved by our institutional review board. An intravitreal off-label bevacizumab injection was recommended. The Spanish Ministry of Health and Consumer Affairs approved compassionate use. Patients were fully informed verbally about the experimental nature of the treatment and they signed an informed consent form.

Cases were recruited from the Hospital Universitari de Bellvitge (Barcelona, Spain) from January–March 2007. Inclusion criteria were: 1) patients aged 50 or older 2) macular edema secondary to nonischemic RVO and 3) VA between 20/400 and 20/50 (Snellen equivalent). Exclusion criteria were: 1) history of retinal surgery or photocoagulation; 2) any history of a thromboembolic event; 3) bleeding disorders; and 4) use of anticoagulative medication other than aspirin. No patient refused treatment.

A comprehensive ophthalmic evaluation was performed; it included a medical history review, best corrected visual acuity testing (using ETDRS charts), slit-lamp biomicroscopy, dilated funduscopic examination using a 78-diopters lens and time domain ocular computed tomography (OCT) (Carl Zeiss Meditec, Dublin, CA, USA) that consisted of an acquisition protocol "Radial lines" (6 linear, 6 mm scans oriented at intervals of 30° and centered on the foveal region). Macular maps were obtained using the "retinal thickness/volume" analysis protocol, and values for central foveal thickness (FT) and total macular volume (MV) were recorded. Follow-up examinations were scheduled at weeks 1, 4, 12, and 24 post-injection, or on demand, if a decrease in VA was noted by the patient. These follow-up examinations used exactly the same procedures as those used in the baseline visit. The incidence of adverse events were monitored throughout the study. The effects of treatment, both on VA and on anatomical changes in the macula shown by OCT, were evaluated. There was no loss of follow-up.

Treatment procedure

Patients received an intravitreal dosage of bevacizumab of 1.25 mg (0.05 mL) at baseline and once every four weeks if OCT indicated macular swelling (quantitatively characterized by a macular thickness larger than 250 microns in any of the six radial scans). All treatments were performed in the office using topical anaesthesia (tetracaine+oxibuprocaine) under sterile conditions. Bevacizumab was injected (using a 30-G needle) through the inferotemporal pars plana, 3.5 mm (pseudophakic) or 4 mm (phakic) posterior to the limbus. A drop of ofloxacine was applied to the affected eye immediately after the procedure and again every 6 hours for 4 days.

Statistical data analysis

All data were collected in an Microsoft Excel 2000 spreadsheet (Microsoft Corporation, Spain). For statistical analysis, the Wilcoxon test was performed. VA measurements were converted to logMAR equivalents to perform analysis. $p < 0.05$ was considered significant.

Results

Twelve patients (seven women and five men) were included. The median age was 66 years and the median duration of symptoms prior to treatment was 4 months. Vein occlusion was located at the inferior branch in six patients and at the superior branch in the remaining six patients. There was a history of hypertension in four patients. All patients completed the 24-week follow-up examination; their baseline characteristics are summarized in Table 1.

Best corrected visual acuity (BCVA) data obtained over the course of the study are summarized in Table 2. Evaluation of BCVA revealed significant improvement at all times compared with baseline. Mean VA improved from 1.32 ± 0.24 (logMAR values) at baseline, to 0.8 ± 0.15 ($p = 0.0003$) at the 6-month follow-up. The macular edema responded promptly, and a reduction in the submacular fluid was observed at the seventh day. At baseline, the mean FT was 615.50 ± 116.29 microns; it declined to 420 ± 72.53 microns ($p = 0.001$). The mean MV improved from 19.81 ± 2.31 mm^3 to 9.23 ± 1.38 mm^3 ($p = 0.0001$) at the 6-month follow-up. Mean changes in parameters recorded by OCT on weeks 1, 4, 12, and 24 post-injection are summarized in Table 3. Overall, four patients were retreated: 2 patients received two consecutive injections of intravitreal bevacizumab, and two patients received three injections. No ocular or systemic adverse events were observed.

Discussion

This study demonstrates the early and clinically relevant benefits of bevacizumab injection for macular edema due to RVO. In this prospective case series, we found that intravitreal

Table 1 Baseline characteristics

Case, age, sex	Affected ye, localization	Duration (months)	logMAR BCVA	OCT FT (microns)	OCT MV (mm^3)
1, 64, F	OD, inferior	2.5	0.63	664	12.91
2, 63, F	OD, inferior	5	1.7	545	22.17
3, 75, M	OD, superior	6	1.05	410	16.65
4, 57, M	OD, superior	3	1.63	667	21.23
5, 67, F	OD, superior	2.5	1.96	601	20.82
6, 66, F	OS, inferior	2	0.62	763	11.9
7, 61 F	OD, superior	3	1.6	495	21.16
8, 75, F	OD, superior	4	1.04	630	15.64
9, 77, M	OS, superior	4	1.62	239	20.22
10, 66, M	OS, inferior	7	1.34	885	12.97
11, 59, M	OS, inferior	6	1.3	498	11.2
12, 79, F	OS, inferior	7	0.96	998	19.81
Median: 66		Median: 4	Median: 1.32	Median: 615.50	Median: 19.81
SD: 7,26		SD: 1.81	SD: 0.43	SD: 205.547	SD: 4.10
Confidence intervals (CI): 4.16		CI: 1.02	CI: 0.24	CI: 116.29	CI: 2.31

Abbreviations: F, female; M, male; SD, standard deviation; OD, right eye; OS, left eye; BCVA, best corrected visual activity; FT, foveal thickness; MV, macular volume.

injections of bevacizumab led both to a significant reduction of FT, as well as to an improvement of visual acuity in patients with RVO. A beneficial effect of intravitreal bevacizumab was observerd as early as the first week and over a 6-month follow-up period.

Our study supports the preliminary results of several recently published papers. The most detailed data on the natural history of CRVO were provided by the Central Vein Occlusion Study Group (CRVO 1995). Clinical outcomes of every new treatment option for CRVO must match with these data. In the natural course of CRVO, only 19% of patients with initial visual acuity of less than 20/200 had a chance of visual acuity of better than 20/200. Patients presenting with initial visual acuity between 20/200 and 20/50 had improvement to better than 20/50 in 19% of cases; in 44% of cases acuity stayed between 20/200 and 20/50. The visual acuity of only 37% of patients became worse than 20/200. Compared with these data, patients treated with intravitreal injections of bevacizumab showed much greater improvement. Priglinger and colleagues (2007) reported improvement in visual acuity from 20/250 at baseline to 20/80 at the 6-month follow-up ($p < 0.001$) in a group of 46 CRVO patients. Mean central retinal thickness decreased from 535 ± 48 microns at baseline to 323 ± 116 microns at the 6-month follow-up (Priglinger et al 2007). In a series of 30 CRVO patients followed for 6 months, Jason and colleagues (2007) reported improvement in VA from 20/394 at baseline to 20/313 at the 3-month follow-up, ($p < 0.05$) and no significant changes after the fourth month. This indicates that bevacizumab represents an effective treatment option for CRVO and that the drug may improve the long-term prognosis of CRVO.

The intravitreal use of bevacizumab may provide anatomical and functional amelioration of the macula in patients with macular edema due to RVO. The electrical responses in the fovea and parafovea of the multifocal electroretinography recording depict a significant improvement at 1 and 3 months after the injection (Moschos and Moschos 2008).

Table 2 logMAR BCVA (baseline and 1, 4 12, and 24 weeks post-injection)

logMAR BCVA baseline	logMAR BCVA, week 1	logMAR BCVA week 4	logMAR BCVA week 12	logMAR BCVA week 24
0.63	0.35	0.17	0.23	0.43
1.7	1.3	0.75	0.77	0.77
1.05	1.01	1.03	1	0.89
1.63	1.47	1.2	1.35	1.17
1.96	0.4	0.43	0.61	0.53
0.62	0.36	0.17	0.23	0.42
1.6	1.2	0.75	0.78	0.76
1.04	1.02	1.02	1	0.86
1.62	1.48	1.3	1.36	1.19
1.34	1	0.78	0.86	0.83
1.3	1.28	1.24	1.28	1.25
0.96	0.5	0.42	0.62	0.56

Note: p (baseline-week 24) = 0.0003
Abbreviation: BCVA, best corrected visual acuity.

Table 3 FT (microns) and MV (mm3) (baseline and 1, 4, 12, and 24 week post-injection)

Case 1	Baseline	Week 1	Week 4	Week 12	Week 24
FT	664	220	166	167	189
MV	12.91	8.48	7.87	8.38	8.34
Case 2					
FT	545	440	165	481	654
MV	22.17	6.96	6.64	9.33	8.35
Case 3					
FT	410	166	496	509	578
MV	16.65	12.17	13.2	13.95	12.95
Case 4					
FT	667	565	459	500	475
MV	21.23	17.32	15.16	15.69	14.63
Case 5					
FT	601	436	175	501	420
MV	20.82	6.66	6.83	9.2	9.5
Case 6					
FT	763	400	170	456	432
MV	11.9	7.47	6.86	7.37	10.56
Case 7					
FT	495	175	195	225	235
MV	21.16	5.95	5.63	8.32	7.35
Case 8					
FT	630	220	460	335	342
MV	15.64	11.16	12.1	12.94	10.55
Case 9					
FT	239	442	336	402	389
MV	20.22	16.31	12.1	14.68	12.48
Case 10					
FT	885	296	450	425	420
MV	12.97	6.25	10.91	10.55	8.95
Case 11					
FT	498	345	450	356	352
MV	11.2	10.72	5.82	10.97	7.55
Case 12					
FT	998	425	182	522	425
MV	19.81	5.55	5.85	8.1	6.98

Notes: p (baseline- week 24): FT = 0.001 MV = 0.0001
Abbreviations: FT, foveal thickness; MV, and macular volume.

Intravitreal injection of triamcinolone acetonide (TA) is another treatment option aimed to reduce macular edema after RVO. Several recent studies report favorable effects of intravitreal injection (4–20 mg) of TA on the course of RVO (Gregory et al 2006). The extent and duration of the effect of intravitreal injection of TA depends on the dose used and the presence of retinal ischemia (Jonas et al 2005). Repeated intravitreal injections of TA are possible; however, after repeated treatments, the effect on reduction of retinal thickness and increase in visual acuity are reduced (Boyd et al 2002; Kupperman et al 2007). Furthermore, although apparently improving the clinical outcome of RVO, repeated intravitreal injections of TA are associated with many potential complications, such as elevated intraocular pressure and cataract formation, which may ultimately decrease the long-term prognosis of RVO (Goff et al 2006). In contrast to intravitreal injection of TA, several injections of bevacizumab appear to have no drug-related complications. However, complications related to repeated intravitreal injections (eg, endophthalmitis, retinal tear, and lens trauma) must be taken into account (Jaissle et al 2006). Fortunately, none of these complications occurred in the present case series; this may be due to the thorough prophylactic, antiseptic regimen applied in our institution to minimize the likelihood of bacterial contamination.

The use of anti-VEGF agents in retinal disease has become increasingly common since the approval (in 2004 and 2006, respectively) of pegaptanib and ranibizumab for age-related maculopathy. These agents are currently being studied for their efficacy against macular edema due to RVO. The anti-VEGF agent most studied in regard to RVO is bevacizumab. Off-label intravitreal injection of bevacizumab was first reported in 2005 to represent a potential therapy for macular edema secondary to CRVO (Rosenfeld et al 2005b). Since then, several additional publications have reported favorable short-term results for reduction of macular edema and improvement of vision in patients with RVO (Spandau et 2006; Pau et al 2007).

Our results suggest a possible short-term benefit for macular architecture and VA; however, it is also clear that such benefits are transient. Continuous VEGF suppression may be required to sustain beneficial effects observed in the short term and the risks associated with multiple intravitreal injections need to be considered. Our data suggest that patients may require several injections to maintain efficacy. Three to four months after the most recent injection, worsening VA was detected in about half of the cases. The data in this study suggest that a single injection of intravitreal bevacizumab has a limited beneficial effect for approximately two months in most patients.

Although VEGF and its receptors represent potential targets for pharmacologic intervention, several important questions remain. Does VEGF play a role in the formation of vascular shunts across ischemic areas? Does continuous blockage of VEGF have a negative effect over the long term? Furthermore, recurrent macular edema may occur in patients

with RVO following treatment with bevacizumab; in some cases, the recurrent macular edema may be more severe than the pre-treatment macular edema (a phenomenon known as "rebound" macular edema) (Matsumoto et al 2007).

The changes observed throughout the present study may provide important clues about drug effects and duration. Favorable macular changes, documented by OCT, were evident as soon as day 7 post-injection. While these improvements were maintained at post-injection week 4, there was a clear tendency for macular edema to recur around week 12; this suggests, therefore, that reinjections might be considered at some point during this period when a 1.25 mg dose regimen is used in setting of ischemic or nonischemic RVO.

The present study does have some limitations that must be recognized: there was no control group; we included only 12 patients and there was only a limited follow-up. However, the promising results reported here indicate that further studies of intravitreal bevacizumab injection for the management of ischemic or nonischemic RVO are justified. Future well-designed studies will help to establish the role of antiangiogenic therapy in the management of RVO.

Disclosure

The authors report no conflicts of interest in this work.

References

Boyd SR, Zachary I, Chakravarthy U, et al. 2002. Correlation of increased vascular endothelial growth factor with neovascularization and permeability in ischemic central vein occlusion. *Arch Ophthalmol*, 120:1644–50.

[CVRO] Central Vein Occlusion Study Group. 1995. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. *Ophthalmology*, 102:1425–33.

Goff MJ, Jumper JM, Yang SS, et al. 2006. Intravitreal triamcinolone acetonide treatment of macular edema associated with central retinal vein occlusion. *Retina*, 26:896–901.

Gregori NZ, Rosenfeld PJ, Puliafito CA, et al. 2006. One-year safety and efficacy of intravitreal triamcinolone acetonide for the management of macular edema secondary to central retinal vein occlusion. *Retina*, 26:889–95.

Hayreh SS. 1983. Classification of central retinal vein occlusion. *Ophthalmology*, 458–74.

Iturralde D, Spaide RF, Meyerle CB, et al. 2006: Intravitreal bevacizumab (avastin) treatment of macular oedema in central retinal vein occlusion: a short-term study. *Retina*, 26:279–84.

Jaissle GB, Ziemssen F, Petermeier K, et al. 2006. Bevacizumab for treatment of macular edema secondary to retinal vein occlusion. *Ophthalmoloe*, 103:471–5.

Jason HSU, Kaiser R, Sivalingam A, et al. 2007. Intravitreal bevacizumab (Avastin) in central retinal vein occlusion. *Retina*, 27:1013–19.

Jonas JB, Akkoyun I, Kamppeter B, et al. 2005. Intravitreal triamcinolone acetonide for treatment of central retinal vein occlusion. *Eur J Ophthalmol*, 15:751–8.

Kuppermann BD, Blumenkranz MS, Haller JA, et al. 2007. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol*, 125:309–17.

Matsumoto Y, Freund KB, Peiretti E. 2007. Rebound macular oedema following bevacizumab (Avastin) therapy for retinal venous occlusive disease. *Retina*, 27:426–31.

Mohamed Q, McIntosh RL, Saw SM, et al. 2007. Interventions for central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*, 114:507–19, 524.

Moschos MM, Moschos M. 2008. Intravitreao use of bevacizumab for macular edeam due to CRVO. A multifocal-ERG and OCT study. *Doc Ophthalmol*, 116:147–52.

Pai SA, Shetty R, Vijayan PB, et al. 2007. Clinical, anatomic, and electrophysiologic evaluation following intravitreal bevacizumab for macular edema in retinal vein occlusion. *Am J Ophthalmol*, 143:601–6.

Priglinger SG, Wolf AH, Kreutzer TC, et al. 2007. Intravitreal bevacizumab injections for treatment of central retinal vein occlusion. Six month results of a prospective trial. *Retina*, 27:1004–12.

Rosenfeld PJ, Fung AE, Puliafito CA. 2005a. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular oedema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging*, 36:336–9.

Rosenfeld PJ, Moshfeghi AA, Puliafito CA. 2005b. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular agerelated macular degeneration. *Ophthalmic Surg Lasers Imaging*, 36:331–7.

Spandau UH, Ihloff AK, Jonas JB. 2006. Intravirreal bevacizumab treatment of macular oedema due to central retinal vein occlusion. *Acta Ophthalmol Scand*, 84:555–6.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/065,847
				Filing Date	August 6, 2018
				First Named Inventor	Yancopoulos, George D.
				Art Unit	1647
				Examiner Name	Jon Lockard
Sheet	1	of	3	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	**2008/0220004**	2008-09-11	Wiegand et al.	
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	BARBAZETTO, "DOSING REGIMEN AND THE FREQUENCY OF MACULAR HEMORRHAGES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH RANIBIZUMAB." Retina, 30:9, 1376-85, 2010	
	2	Bayer Investor News, "Bayer and Regeneron Start additional Phase 3 Study for VEGF Trap=Eye in Wet Age-related Macular Degeneration." May 8, 2008	
	3	BOYER, "A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration." Opthalmology, 116:9, 1731-39, September 2009.	
	4	BROWN, "Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration." N Engl J Med 355:14, 1432-44, October 5, 2006	
	5	BROWN, "Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration." Ophthalmology, 118:6, 1089-97, June 2011.	
	6	BROWN, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 2013.	
	7	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion." Ophthalmology, 2010.	
	8	CAMPOCHIARO, "Sustained Benefits from Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a phase III Study." Ophthalmology, 188:10, 2041-49, October 2011.	
	9	CSAKY, "Safety Implications of Vascular Endothelial Growh Factor Blockade for Subjects Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Therapies." Am. J. Ophthalmology, 148:5, 647-56, November 2009.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/065,847
				Filing Date	August 6, 2018
				First Named Inventor	Yancopoulos, George D.
				Art Unit	
				Examiner Name	
Sheet	2	of	3	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	10	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 2012.	
	11	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, June 2010, available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
	12	ENGELBERT, "LONG-TERM FOLLOW-UP FOR TYPE 1 (SUBRETINAL PIGMENT EPITHELIUM) NEOVASCULARIZATION USING A MODIFIED 'TREAT AND EXTEND' DOSING REGIMENT OF INTRAVITREAL ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY." Retina, 30:9, 1368-75, 2010	
	13	ENGELBERT, "'TREAT AND EXTEND' DOSING OF INTRAVITREAL ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR TYPE 3 NEOVASCULARIZATION/RETINAL ANGIOMATOUS PROLIFERATION." Retina, 29:10, 1424-31, 2009	
	14	Eylea®, Highlights of Prescribing Information, Revised 08/2018.	
	15	FUNG, "An Optical Coherence Tomography-Guided, Variable Dosing Regiment with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration." Am J Ophthalmology 143:4, 566-83, April 2007	
	16	GALE, "Complementary and Coordinated Roles of the VEGFs and Angiopoietins during Normal and Pathologic Vascular Formation." Cold Spring Harbor Symposia on Quantitative Biology, Volume LXVIL, pp. 267-73, 2002.	
	17	GARCIA-QUINTANILLA, "Pharmacokinetics of Intravitreal Anti-VEGF Drugs in Age-Related Macular Degeneration." Pharmaceutics, 11:365, 2019.	
	18	GOMEZ-MANZANO, "VEGF Trap induces antiglioma effect at different stages of disease." Society for Neuro-Oncology, December 2008.	
	19	GRAGOUDAS, "Pegaptanib for Neovascular Age-Related Macular Degeneration." N Engl J Med 351:27, 2805-16, December 30, 2004	
	20	HEIER, "Intravitreal Aflibercept for Diabetic Macular Edema." Ophthalmology, 2016.	
	21	Ho et al., Slides entitled CLEAR IT 2 One-Year Key Results, Retina Society 2008	
	22	KARIA, Niral, "Retinal vein occlusion: pathophysiology and treatment options" Clinical Ophthalmology, 4:809-816 (2010)	
	23	KOROBELNIK, "Intravitreal Aflibercept for Diabetic Macular Edema." Ophthalmology, 121:11, 2247-54, November 2014.	
	24	LALWANI, "All About PrONTO: Study Yielded Good Results in AMD With Treatment Guided by OCT." Retina Today, May 2007	
	25	LALWANI, 'A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-related Macular Degeneration: Year 2 of the PrONTO Study." Am J Ophthalmology, 148:1, 43-58, July 2009.	
	26	LEVINE, "MACULAR HEMORRHAGE IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION AFTER STABILIZATION WITH ANTIANGIOGENIC THERAPY." Retina, 29:8, 1074-79, 2009.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/065,847
				Filing Date	August 6, 2018
				First Named Inventor	Yancopoulos, George D.
				Art Unit	
				Examiner Name	
Sheet	3	of	3	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	27	MARGOLIS, "HEMORRHAGIC RECURRENCE OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION NOT PREDICTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY." Retinal Cases & Brief Reports, 4:1, 2010	
	28	MASSIN, "Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study*)." Diabetes Care, 33:11, 2399-405, November 2010.	
	29	MITCHELL, "The RESTORE Study, Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema." Ophthalmology, 188:4, 615-25, April 2011.	
	30	NGUYEN, "Ranibizumab for Diabetic Macular Edema, Results from 2 Phase III Randomized Trials: RISE and RIDE." Ophthalmology, 119:4, 789-801, April 2012.	
	31	Regeneron Press Release, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration." May 8, 2008	
	32	Regeneron Press Release, "VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients With Diabetic Macular Edema." February 18, 2010	
	33	ROSENFELD, "Ranibizumab for Neovascular Age-Related Macular Degeneration." N Engl J Med, 355:14, 1419-31, October 5, 2006.	
	34	ROSENFELD, "Lessons Learned From Avastin and OCT-The Great, the Good, the Bad, and the Ugly: The LXXV Edward Jackson Memorial Lecture." Am. J. Ophthalmology, 204:26-45, August 2019.	
	35	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration." Ophthalmology, 2010.	
	36	SCHMIDT-ERFURTH, "Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema." Ophthalmology, 121:5, 1045-53, May 2014	
	37	SPAIDE, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." Am J Ophthalmology, April 2007.	
	38	WOLFSON, "Regeneron Focuses on Age-Related Macular Degeneration." Chemistry & Biology 15:303-304, April 2008	
	39	YANCOPOULOS, "Vascular-specific growth factors and blood vessel formation." Nature 407:242-48, September 14, 2000.	
	40	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143, October 1, 2010.	
	41	YUNG, "moving Toward the Next Steps in Angiogenesis Therapy?" Society for Neuro-Oncology, 10:939, 2008	

Examiner Signature	/JON M LOCKARD/	Date Considered	11/25/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

/J.L./

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

=> DIS HIST

(FILE 'HOME' ENTERED AT 17:52:47 ON 05 DEC 2019)

FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 17:52:55 ON 05 DEC 2019

```
L1         12891 S (VEGF (W) TRAP) OR AFLIBERCEPT
L2          1134 S L1 (S) (MACULAR (W) EDEMA)
L3           358 S L2 (P) (RETINAL (W) VEIN (W) OCCLUSION)
L4           185 DUP REM L3 (173 DUPLICATES REMOVED)
                 E YANCOPOULOS G D/AU
L5          2109 S E3-E7
L6             2 S L4 AND L5
L7            28 S L4 AND 2 (W) MG
```

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Dec 10, 2019 03:34:43 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
16055847	CTNF	12/10/2019	REGN-008CIPCON3
	892	12/10/2019	REGN-008CIPCON3
	1449	12/10/2019	REGN-008CIPCON3
	1449	12/10/2019	REGN-008CIPCON3
	1449	12/10/2019	REGN-008CIPCON3
	1449	12/10/2019	REGN-008CIPCON3
	1449	12/10/2019	REGN-008CIPCON3

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Electronically filed 1/23/2020		
AMENDMENT UNDER 37 C.F.R. §1.111	Attorney Docket No.	REGN-008CIPCON3
	Confirmation No.	3451
	First Named Inventor	George D. Yancopoulos
	Application Number	16/055,847
	Filing Date	August 6, 2018
Address to:	Group Art Unit	1647
Mail Stop AMENDMENT	Examiner Name	Jon McClelland Lockard
Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This amendment is responsive to the Office Action dated December 10, 2019, for which a three-month period for response was given, making this response due on March 10, 2020. Accordingly, this response is timely filed.

In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

AMENDMENTS TO THE CLAIMS

1. - 20. (**Canceled**)

21. (**Previously Presented**) A method for treating macular edema following retinal vein occlusion in a human subject comprising administering 2 mg aflibercept to the subject by intravitreal injection once every 4 weeks.

22. (**Previously Presented**) The method of claim 21 wherein the aflibercept is administered in a volume of 0.05 ml.

23. (**Previously Presented**) The method of claim 22 wherein the aflibercept is in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier.

REMARKS

Formal Matters

Claims 21-23 are now pending in this application.

Claims 1-20 were previously canceled without prejudice.

No new matter has been added.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a non-final Office Action was mailed October 1, 2019.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

Rejection under 35 U.S.C. §102

Claims 21 and 23 were rejected 35 U.S.C. §102 as anticipated by the publication dated November 13, 2009 referring to a proposed clinical trial.

The rejection is respectfully traversed and its reconsideration requested in view of the following.

The Examiner alleged that the claims were anticipated by a posting on the clinicaltrials.gov website which was published November 13, 2009 ("Clinical Trial"). The Applicants disagree. The clinicaltrials.gov posting cited by the Examiner was not published on November 13, 2009. The cited art appears to be a summary page relating to the clinical trial which was published on a later date. Page 7 of

the cited art summarizes the history of the clinical trial and its various updates. See below:

Responsible Party:	Bayer
ClinicalTrials.gov Identifier:	NCT01012973 History of Changes
Other Study ID Numbers:	14130
	2009-010973-19 (EudraCT Number)
First Posted:	November 13, 2009 Key Record Dates
Results First Posted:	November 22, 2012
Last Update Posted:	November 3, 2014
Last Verified:	October 2014

Since this summary cites the date, November 3, 2014, as the Last Update Posted, it would appear that the publication date of this webpage was on or after this date. Since the filing dates of the instant application pre-date November 3, 2014, this art is not properly citable prior art.

Furthermore, the posting which was published on November 13, 2009, which has been cited herein in an Information Disclosure Statement, did not disclose administering 2 mg of aflibercept each month. Thus, the claims would also be novel over the November 13, 2009 posting. The Applicants request withdrawal of the rejection.

Rejection under 35 U.S.C. §103

Claim 22 was rejected under 35 U.S.C. §103 as unpatentable over the November 13, 2009 publication further in view of Gutierrez et al.

Since the Examiner's characterization of Clinical Trial was not accurate, the reasons for rejecting the claims over Clinical Trial and Gutierrez are not applicable. In any event, the claims are patentable over the November 13, 2009 posting and Gutierrez *et al.* At the time of the invention, the amount of aflibercept which must be administered each month in order to treat a patient suffering from DME after RVO could not have been predicted based on the November 13, 2009 posting. Gutierrez *et al.* provided no further suggestion of the claimed amount and dosing frequency of aflibercept. Instead, Gutierrez *et al.* related to an anti-VEGF antibody (bevacizumab) which was dosed at a lower amount, 1.25 mg. Any suggestion of such a dosing amount and frequency could only have come from the instant specification. This, however, would require impermissible hindsight reconstruction. The Applicants request withdrawal of the rejection.

In view of the above the rejection is believed to have been overcome and its reconsideration and withdrawal is respectfully requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON3.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 23, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Electronic Acknowledgement Receipt

EFS ID:	38382077
Application Number:	16055847
International Application Number:	
Confirmation Number:	3451
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON3
Receipt Date:	23-JAN-2020
Filing Date:	06-AUG-2018
Time Stamp:	16:15:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-008CIPCON3_Amend_OA_2020-01-23.pdf	49517 185b4c7061baec1cbdacdadfa453b4a3f8889318	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	5
Warnings:			
Information:			
	Total Files Size (in bytes):	49517	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/055,847	Filing Date 08/06/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	01/23/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 3	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TINA J BARDEN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	16/159,282 – Third Party Submissions dated May 31, 2019	
	2	BROWN, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 120(10):2013-22 (October 2013)	
	3	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion: six-month primary end point results of a phase III study." Ophthalmology, 117(6):1102-1112 (June 2010)	
	4	DIXON et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" Expert Opin. Investig. Drugs, 18(10):1573-1580 (2009)	
	5	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 119(8):1658-65 (2012)	
	6	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, Issue 42, (June 2010) available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
	7	GOMEZ-MANZANO, "VEGF Trap induces antiglioma effect at different stages of disease." Neuro-Oncology, 10:940-945 (December 2008)	
	8	HEIER, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies." Ophthalmology, 123(11):2376-2385 (November 2016)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973) (NOTE: May correspond to "Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**" which was cited in the Third Party Observations dated 05/01/19)	
	10	KAISER, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema." Br. J. Ophthalmol, 93(2):135-36 (February 2009)	
	11	MARGOLIS, "Hemorrhagic Recurrence Of Neovascular Age-Related Macular Degeneration Not Predicted By Spectral Domain Optical Coherence Tomography." Retinal Cases & Brief Reports, 4:1-4 (2010)	
	12	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 2003)	
	13	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCIE Study" Ophthalmology, 118(5)831-839 (2010)	
	14	SCHNICHELS, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." Br. J. Ophthalmol., 97:917-923 (2013)	
	15	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, 32(8):1556-1562 (August 2009)	
	16	SPAIDE, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." Am J Ophthalmology, 143(4):679-680 (April 2007)	
	17	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR] NOTE:** May correspond to **"**Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973)" cited by the Examiner in the Office Action dated 12/10/19 in USSN 16/055,847	
	18	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143:13-16 (October 1, 2010)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 05/31/2019

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/31/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/159,282	10/12/2018	Yancopoulos, George D.	REGN-008CIPCON4

	EXAMINER	
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065	MARIANNE C SEIDEL	
	ART UNIT	PAPER
	1600	20190529

DATE MAILED: _____

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The third-party submission under 37 CFR 1.290 filed on 5/28/19 for the instant application has been determined to be compliant with 35 U.S.C. 122(e) and 37 CFR 1.290 and is being entered in the application. Please allow a few days for the submission to be visible in the Patent Application Information Retrieval (PAIR) system.

/MARIANNE C SEIDEL/
Quality Assurance Specialist, Art Unit 1600

PTO-90C (Rev.04-03)

Concise Description of Relevance

VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration

James A. Dixon et al. *Expert Opin. Investig. Drugs* (**2009**) 18(10):1573-1580 (hereafter "Dixon")

Dixon is prior art under pre-AIA §102(b) because it published more than one year before the earliest effective filing date (January 13, 2011) of U.S. Application No. 16/159,282 (hereafter "the '282 application).

U.S. Application No. 16/159,282	Relevant disclosure in Dixon
21. A method for treating an angiogenic eye disorder in a patient, said method comprising	**Dixon** is related to clinical trial results of treating neovascular age-related macular degeneration (wet AMD) with VEGF Trap-eye. Wet AMD is an angiogenic eye disorder. *See e.g.*, ***Background/p. 1573***, disclosing that aflibercept (VEGF Trap-eye) is a promising therapy for AMD by interrupting angiogenesis. *See also* the definition of "angiogenic eye disorder" in the '282 application (para. [0004]).
sequentially administering to the patient a single **initial dose** of a VEGF antagonist, followed by one or more **secondary doses** of the VEGF antagonist, followed by **one or more tertiary doses** of the VEGF antagonist;	Phase II trial ***(§2.6.2, p. 1576***) teaches that patients with CNV (subfoveal choroidal neovascularization), a subtype of AMD, received monthly dose of 0.5mg or 2mg for 12 weeks (0, 4, 8, 12) followed by treatment of the same dose on a PRN basis. Thus, DIXON teaches AMD patients being treated by (1) a **single initial dose** of 0.5mg or 2mg at **week 0**, followed by **3 secondary doses** in 4-week intervals (*i.e.*, on **week 4, 8 and 12 after the initial dose**); followed by **tertiary doses** on **PRN basis**. **Dixon** further teaches criteria for re-dosing, including basis on visual (ETDRS letters) or anatomical (retinal thickness by OCT).
wherein each secondary dose is administered **4 weeks after the immediately preceding dose**; and	
wherein each **tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional**;	
wherein the **VEGF antagonist** is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF	VEGF Trap-eye is a VEGF antagonist having key binding domains of human VEGFR-1 and -2 combined with a human

receptor, and a multimerizing component.	IgG Fc fragment. (***§2.2, p 1575***)
22. The method of claim 21, wherein the VEGF antagonist is **aflibercept**.	VEGF Trap-eye is chemically identical to aflibercept. (***§2.3, p 1575***)
23. The method of claim 22, wherein all doses of the VEGF antagonist are administered to the patient by **intraocular** administration.	Phase II trial *(**§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in one eye (*i.e.*, intraocular administration). **Dixon** teaches intravitreal injection throughout.
24. The method of claim 23, wherein the intraocular administration is **intravitreal** administration.	Phase II trial *(**§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in one eye (*i.e.*, intraocular administration). **Dixon** teaches intravitreal injection throughout.
25. The method of claim 24, wherein all doses of the VEGF antagonist comprise from about **0.5 mg** to about **2 mg** of the VEGF antagonist.	Phase II trial *(**§2.6.2, p. 1576***) teaches AMD patients received VEGF Trap-eye in 0.5mg or 2mg per dose.
28. The method of claim 27, wherein the angiogenic eye disorder is selected from the group consisting of: **age related macular degeneration**, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.	AMD is an angiogenic eye disorder.
29. The method of claim 28 wherein the angiogenic eye disorder is age related macular degeneration.	AMD is an angiogenic eye disorder.
30. The method of claim 28 wherein the angiogenic eye disorder is diabetic retinopathy.	VEGF Trap-Eye was used to treat diabetic retinopathy (***§2.6.1, p1575, the third paragraph***).
31. The method of claim 28, wherein the angiogenic eye disorder is diabetic macular edema.	VEGF Trap-Eye was used to treat diabetic macular edema *(**§2.6.1, p1575, the fourth paragraph***).

Concise Description of Relevance

Enrollment Completed in Regeneron and Bayer HealthCare Two Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)

Regeneron Press Release dated **September 14, 2009** (hereafter "**Regeneron**")

https://newsroom.regeneron.com/static-files/661111b9-3da3-459b-b0da-c74f00ab4b32

Regeneron is prior art under pre-AIA §102(b) because it published more than one year before the earliest effective filing date (January 13, 2011) of U.S. Application No. 16/159,282 (hereafter "the '282 application."

U.S. Application No. 16/159,282	Relevant disclosure in Regeneron (with evidentiary support from Dixon)
32. A method for treating an angiogenic eye disorder in a patient, said method comprising	**Regeneron** discloses the VIEW Program, which included Phase 3 studies for treating neovascular age-related macular degeneration (wet AMD). Wet AMD is a known angiogenic eye disorder. *See also* definition of "angiogenic eye disorder" in the '282 application (para. [0004]).
sequentially administering to the patient a **single initial dose** of a VEGF antagonist, followed by **one or more secondary doses** of the VEGF antagonist, followed by **one or more tertiary doses** of the VEGF antagonist;	The VIEW Program teaches patients with wet AMD are to receive regular doses of 0.5mg or 2mg VEGF Trap-eye at 4-week intervals in the first year, followed by continued treatment for another year on a flexible, criteria-based extended PRN regimen with a dose administered ***at least every 12 weeks***, but not more often than every four weeks. Thus, **Regeneron** teaches AMD patients being treated by (1) a ***single initial dose*** of 0.5mg or 2mg, followed by (2) ***secondary doses at 4-week intervals*** for a year, followed by (3) treatment for another year based on a flexible schedule, which would include ***at least one tertiary dose at 12-week*** from the immediately preceding dose. *See also*, Example 4 of the '282 application, which tracks closely to the VIEW program. Example 4 provides the written support for the dosing regimen recited in claim 32.
wherein each secondary dose is administered **4 weeks** after the immediately preceding dose; and	
wherein each tertiary dose is administered **12 weeks** after the immediately preceding dose;	
wherein the VEGF antagonist is a receptor-	VEGF Trap-eye is an anti-VEGF agent, a soluble

based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.	VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PIGF). *See* "About VEGF Trap-Eye; *see also* evidentiary support in **Dixon**.
33. The method of claim 22*, wherein the VEGF antagonist is **aflibercept**. * *It appears that claim 32 was intended.*	VEGF Trap-eye is chemically identical to aflibercept. *See also* evidentiary support in **Dixon (*§2.3, p 1575*)**.
34. The method of claim 23*, wherein all doses of the VEGF antagonist are administered to the patient by **intraocular** administration. * *It appears that claim 33 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye "on maintaining and improving vision when dosed as an ***intravitreal*** injection…" *See* the first paragraph. Intravitreal injection is a type of intraocular administration.
35. The method of claim 23*, wherein the intraocular administration is **intravitreal** administration. * *It appears that claim 33 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye "on maintaining and improving vision when dosed as an ***intravitreal*** injection…" *See* the first paragraph of page 1.
36. The method of claim 25*, wherein all doses of the VEGF antagonist comprise from about **0.5 mg** to about **2 mg** of the VEGF antagonist. * *It appears that claim 35 was intended.*	The VIEW program evaluates the effect of VEGF Trap-eye of two dosing strengths (0.5mg and 2mg) administered on regular schedules. *See* paragraph 1 and paragraph 4 on page 1.
37. The method of claim 36, wherein all doses of the VEGF antagonist comprise **0.5 mg** of the VEGF antagonist.	
38. The method of claim 36, wherein all doses of the VEGF antagonist comprise **2 mg** of the VEGF antagonist.	
39. The method of claim 36, wherein the angiogenic eye disorder is selected from the group consisting of: **age related macular degeneration**, diabetic retinopathy, **diabetic macular edema**, **central retinal vein occlusion**, branch retinal vein occlusion, and	**Regeneron** teaches that VEGF Trap-eye is used for treating eye diseases, including wet AMD, diabetic macular edema (DME), and Central Retinal Vein Occlusion (CRVO). *See* the second paragraph on page 1.

corneal neovascularization.	
40. The method of claim 39 wherein the angiogenic eye disorder is age related macular degeneration.	**Regeneron** teaches treating AMD throughout.
41. The method of claim 39 wherein the angiogenic eye disorder is diabetic retinopathy.	**Regeneron** teaches that the primary endpoint is evaluated using the standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart for visual acuity, suggesting that an effective therapy for treating AMD could also be used to treat diabetic retinopathy.
42. The method of claim 39, wherein the angiogenic eye disorder is diabetic macular edema.	**Regeneron** teaches VEGF Trap-eye is also for treatment of diabetic macular edema. *See* the second paragraph on page 2.

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	16159282

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance

U.S. PATENT APPLICATION PUBLICATION

Cite No	Publication Number	Concise Description of Relevance

FOREIGN PATENT DOCUMENTS		
CiteNo	**Foreign Document Number**	**Concise Description of Relevance**

NON-PATENT PUBLICATIONS		
Cite No	**Reference**	**Concise Description of Relevance**
1	Regeneron Press Release dated September 14, 2009	See Attached

2	James A. Dixon et al., Expert Opin. Investig. Drugs (2009) 18(10):1573-1580	See Attached

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
						☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)			
Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

1	James A. Dixon et al., Expert Opin. Investig. Drugs (2009) 18(10):1573-1580	☐	☐
2	Regeneron Press Release dated September 14, 2009	☐	☐

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

☐ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☒ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16159282

Signature	/Michael Berry/		
Name/Print	Michael Berry	Registration Number (if applicable)	

Examiner Signature		Date Considered	

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Electronic Acknowledgement Receipt

EFS ID:	36133892
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	
First Named Inventor/Applicant Name:	
Correspondence Address:	-
Filer:	Michael Berry
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	28-MAY-2019
Filing Date:	
Time Stamp:	18:48:57
Application Type:	

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Expert_Opinion_2009_Dixon.PDF	309524 2c3c83ba00e8ab387c5811f4e8a8cd525b78e5c8	no	8
Warnings:					
Information:					
2	Non Patent Literature	REGN_News_2009_9_14_General_Releases.PDF	19451 e3bd0705cfeb86d02dd060253ce18d308faa9985	no	2
Warnings:					
Information:					
3	Concise Description of Relevance	Concise_Description_of_Relevance_Dixon.pdf	126013 799231529e1c7dc8e3ca6157997f40484631c099	no	2
Warnings:					
Information:					
4	Concise Description of Relevance	Concise_Description_of_Relevance_Regeneron.pdf	129770 e0e1d202349cb183cbcc9d2d4a02388680c27991	no	3
Warnings:					
Information:					
5	Concise Description of Relevance	Concise-description-generated.pdf	29880 ae58db77ab1df26a286651d7edc3d47bd40693a5	no	3
Warnings:					
Information:					
6	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	42846 a9a51a283af49cfe20e69f4f802c10f06a583271	no	3
Warnings:					
Information:					
7	Request for Notification of Non-compliant Third-Party Submission	Third-party-notification-request.pdf	19739 7952fd2c976baa92be77b598e0026bbcd475d8a4	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	677223

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Vascular endothelial growth factor Trap-Eye for diabetic macular oedema

Peter K Kaiser

Diabetic macular oedema (DMO) is the leading cause of visual loss in working-aged Americans, and as such successful treatment is of major public health importance. The gold standard is laser photocoagulation based on the landmark Early Treatment Diabetic Retinopathy Study (ETDRS).[1] In the ETDRS, laser treatment reduced the 3-year risk of moderate visual loss by 50%; however, the standard teaching is that patients in the ETDRS rarely improved vision. In fact, in the published ETDRS manuscripts to date, only around 10% of patients gained more than three lines of vision. This led to the prevailing thinking that laser prevents vision loss, but rarely results in visual improvement. Thus, newer therapies have been explored in an effort to improve outcomes in this common and devastating condition.

Vascular endothelial growth factor (VEGF) was one of the first cytokines implicated in diabetic retinopathy and DMO with elevated VEGF levels found in patients with active disease.[2] Increased retinal capillary permeability due to breakdown of the blood–retina barrier have been shown to be mediated by VEGF.[3] Thus, VEGF appears to be a good target to prevent DMO and progression of diabetic retinopathy.

Several anti-VEGF agents have been evaluated in off-label case series and small-scale clinical trials to treat DMO. In a randomised, phase 2 clinical trial of 172 patients, pegaptanib (Macugen, Eyetech, New York), a VEGF165 specific blocker, resulted in a mean improvement in vision of +4.7 letters with 34% gaining 10 letters of more at 36 weeks.[4] Similarly, the randomised, phase 2 DRCR.net trial of 121 patients with bevacizumab (Avastin, Genentech, South San Francisco, California), a pan-VEGF antibody, reported a mean improvement in vision of +5 letters with 33% having greater than 10 letters of improvement at 12 weeks.[5] Finally, the phase 1/2 Ranibizumab for (O)edema of the Macula in Diabetes (READ) study evaluated ranibizumab (Lucentis, Genentech), an antibody fragment that blocks all forms of VEGF, and reported +12.3 letters of visual improvement at month 7. A pivotal Phase 3 trial testing ranibizumab for DMO is currently under way. In this issue ***(see page 144)***, another VEGF blocker has shown early success in the management of DMO—VEGF Trap-Eye.[6]

Traps consist of two extracellular cytokine receptor domains fused together to a human immunoglobulin G (IgG).[7] VEGF Trap-Eye is a soluble fusion protein that combines ligand-binding elements taken from the extracellular components of VEGF receptors 1 and 2 fused to the Fc portion of IgG1.[8] This protein contains all human amino acid sequences, which minimises the potential for immunogenicity in human patients. Similar to bevacizumab and ranibizumab, VEGF Trap-Eye blocks all isoforms of VEGF and placental growth factor. In the small phase 1, open-label study by Do and colleagues, five patients with DMO were treated with VEGF-Trap Eye with good short-term results and safety.

One may ask why one should develop another extracellular VEGF blocker when we already have bevacizumab and ranibizumab. VEGF Trap-Eye has several features that make it appealing in comparison with the currently available therapeutics. The key feature is the binding constant for VEGF is approximately 0.5 pM Kd, considerably higher than ranibizumab, bevacizumab or even native VEGF receptors. This higher binding affinity translates into greater activity at lower biological levels, and consequently a longer duration of action. Some studies have suggested as long as 10 weeks.[9] This longer duration is very important, as diabetic retinopathy is a chronic condition, and most patients are working. All the anti-VEGF DMO studies to date indicate that when the therapy was stopped, vision returned to baseline, and any gains in retinal thickness and fluorescein leakage were reversed. Thus, continuous treatment may be necessary to maintain the improvements in outcomes. These repeated intravitreal anti-VEGF injections will put a strain on both the healthcare system and patients.

With all anti-VEGF agents, systemic safety needs to be evaluated. All known anti-VEGF therapeutics are detectable in the systemic circulation, often with levels high enough to block all native VEGF. Concerns have been raised about systemic effects including stroke, myocardial infarction and hypertension. Current anti-VEGF studies have been too small to truly evaluate the safety of these drugs in the general population. While a recent meta-analysis with all the randomised ranibizumab studies failed to reveal any increased risk of these events, it also does not mean there is not an increased risk, and we all need to be cognisant of this fact (D Boyer, American Academy of Ophthalmology Meeting, Atlanta, Georgia, 2008).

Finally, one important fact overlooked by many in the ETDRS results and more importantly in the statistical planning for many current clinical trials for DMO is that 85% of the patients in the ETDRS could not improve three lines, since they had vision better than 20/40 at the start of the study.[1] In fact, in a subset of 105 ETDRS patients with definite centre thickening on fundus photographs, less severe retinopathy and a visual acuity letter score <20/32 at baseline, the median change in the visual acuity letter score was +4 letters, with 30% improving 10 or more letters at 2 years.[10] Similarly, the DRCR.net reported at 2 years a mean improvement of 1 letter with 18% gaining three or more lines.[10] So, our old standby, laser, really works better than we thought! All studies with anti-VEGF to date have been too short to truly evaluate the long-term efficacy of this treatment. The DRCR.net showed us that a treatment we thought was better than laser was only better in the short term, and long-term follow-up was necessary to actually show the benefit of laser over steroids in this particular patient population. Thus, we need to wait for the results of ongoing studies with longer follow-up before we declare anti-VEGF therapy a new paradigm in DMO management.

The addition of VEGF-Trap Eye as a possible treatment for DMO is exciting, as it has some appealing features over current anti-VEGF therapies. However, our enthusiasm has to be tempered by

Correspondence to: Dr Peter K Kaiser, Digital OCT Reading Center, 9500 Euclid Ave, Desk i3, Cleveland, OH 44195, USA; pkkaiser@aol.com

the short-term nature of this study, the theoretical risks of anti-VEGF therapy and the possible need for continuous therapy to achieve visual gains. Nevertheless, there are many patients who do not respond to laser, and continued exploration into new treatments and even treatment combinations is warranted.

Funding: None.

Competing interests: PKK's employer, the Cole Eye Institute, has received research grant support from Genentech on his behalf. PKK serves on the Scientific Advisory Boards of Genentech and Regeneron. His participation in these boards has been approved and disclosed to the Cleveland Clinic's Conflict of Interest Committee.

Br J Ophthalmol 2009;**93**:135–136.
doi:10.1136/bjo.2008.144071

REFERENCES

1. **Early Treatment Diabetic Retinopathy Study Group.** Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 1. *Arch Ophthalmol* 1985;**103**:1796–806.
2. **Adamis AP,** Miller JW, Bernal MT, *et al.* Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 1994;**118**:445–50.
3. **Antonetti DABA,** Hollinger LA, Wolpert EB, *et al.* Vascular endothelial growth factor induces rapid phosphorylation of tight junction proteins occludin and zonula occluden 1. A potential mechanism for vascular permeability in diabetic retinopathy and tumors. *J Biol Chem* 1999;**274**:23463–76.
4. **Cunningham ETJ,** Adamis AP, Altaweel M, *et al.* A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 2005;**112**:1747–57.
5. **Diabetic Retinopathy Clinical Research Network.** A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;**114**:1860–7.
6. **Do DV,** Nguyen QD, Shah SM, *et al.* Campochiaro. An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor trap-eye in patients with diabetic macular oedema. *Br J Ophthalmol* 2009;**93**:144–9.
7. **Economides AN,** Carpenter LR, Rudge JS, *et al.* Cytokine traps: multi-component, high-affinity blockers of cytokine action. *Nat Med* 2003;**9**:47–52.
8. **Holash J,** Davis S, Papadopoulos N, *et al.* VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci USA* 2002;**99**:11393–8.
9. **Stewart MW,** Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol* 2008;**92**:667–8.
10. **Diabetic Retinopathy Clinical Research Network.** A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;**115**:1447–9.

Cover illustration

Lord Shiva's third eye

The cover illustration depicts the Lord Shiva, the third god of the Hindu Trinity (Trimurti), represented by Lord Brahma, Lord Vishnu and Lord Shiva, the Creator, the Preserver and the Destroyer of the universe, respectively. Some contend that the word "destroyer" is used in error as dissolution for creation, as autumn is to spring, is an essential part of the cyclic process of creation, preservation, dissolution and re-creation.

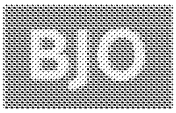
The image of Shiva, as portrayed among Hindus, contains common symbols representative of his superiority. One of these symbols is his third eye, seen in the centre of his forehead; hence he is often referred to as Tryambaka Deva (literally meaning "three-eyed lord"). His right eye is believed to be the sun, the left eye is the moon and his third eye represents fire. His left and right eyes indicate his activity in the physical world. Often Shiva is shown with half open eyes, signifying the never ending, ongoing nature of the birth and destruction of the universe. When the eyes are completely closed it signifies the dissolution of the universe and when it is completely open a new cycle of creation begins.

The third eye can detect evil, even when it is not immediately apparent and the fire that emanates from it can annihilate evil. It also symbolises his activity in the metaphysical, spiritual world and represents the power of knowledge. This eye is seen to be the source of his untamed energy. Once while Shiva was in the midst of worship, the love god, Kama, distracted him. In his anger he opened his third eye, and fire from the eye devoured Kama, until Parvati (Shiva's wife, also known as Kali mata) saved him. For these reasons Shiva is seen as the "destroyer". The power of this eye is so great that it is feared by wrongdoers.

It is said to have appeared when Parvati playfully blindfolded him with her two hands, while he was deep in meditation. Immediately the universe plunged into darkness and chaos reigned supreme. To prevent impending catastrophe, Shiva formed a third eye from which fire emerged to recreate light and order, hence saving the world from inevitable disaster. Throughout imagery of Shiva this eye is depicted as closed or by three horizontal lines in the middle of his forehead. Many Hindus wear a tilak between the eyebrows to represent the third eye, as it is seen as a sign of enlightenment.

Lord Shiva is always shown with a snake (Vasuki Naga, symbol of yogic powers) coiled three times (for the past, present and future) around his neck.

Neeru Dhillon, Arun D Singh, Harminder S Dua



Vascular endothelial growth factor Trap-Eye for diabetic macular oedema

Peter K Kaiser

Br J Ophthalmol 2009 93: 135-136
doi: 10.1136/bjo.2008.144071

Electronic Patent Application Fee Transmittal

Application Number:	16055847
Filing Date:	06-Aug-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON3

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	38404957
Application Number:	16055847
International Application Number:	
Confirmation Number:	3451
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON3
Receipt Date:	27-JAN-2020
Filing Date:	06-AUG-2018
Time Stamp:	13:35:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	E20201QD36408129
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	0725US04_2020-01-27_Supp_IDS_trans_REGN-008CIPCON3.pdf	51227 3c62e336e6fd28f6128045ff48b27e170d6501e8	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0725US04__2020-01-27_Supp_IDS_SB08A.pdf	39286 49083dc00544a36daacea16658a31927da7fa5ff	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	16159282_Third_Party_Observations_2019-05-31.pdf	466996 706ec204df289be96f42875a8b7bbc473af07aab	no	16
Warnings:					
Information:					
4	Non Patent Literature	Kaiser_2009.pdf	110354 baf234a0282d39fd7d1a30e5e5eec6d01f056d2f	no	3
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30914 cd4d6cf67f286da2236b2561c2f0386462b2052f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	698777		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT		
	Attorney Docket No.	REGN-008CIPCON3
	Confirmation No.	3451
	First Named Inventor	George D. Yancopoulos
	Application Number	16/055,847
	Filing Date	August 6, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such.

A listing of the documents is shown on enclosed Form PTO/SB/08A. All documents with the exception of documents (1) and (10) in the non-patent literature were previously submitted and copies are not enclosed. These documents are being relisted on the PTO/SB/08A form to complete the NPL cite from the originally submitted version, for example, article submitted while "In Press".

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by

any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON3.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 27 January 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	4	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01182013_27424.1)	
	2	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01252011_27433.1)	
	3	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01262012_27428.1)	
	4	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01302013_27423.1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	4	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	5	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02092010_27442.1)	
	6	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02202012_27427.1)	
	7	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_03162010_27441.1)	
	8	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04082011_27432.1)	
	9	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04162010_27440.1)	
	10	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_06232011_27431.1)	
	11	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_07222010_27439.1)	
	12	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08252010_27438.1)	
	13	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08262010_27437.1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	3	of	4	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	14	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09082010_27436.1)	
	15	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09192011_27430.1)	
	16	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10042010_27435.1)	
	17	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10232012_27426.1)	
	18	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10272013_27422.1)	
	19	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11012010_27434.1)	
	20	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11132009_27444.1)	
	21	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11292011_27429.1)	
	22	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12182012_27425.1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	4	of	4	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	23	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12212010_27443.1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: January 18, 2013 (v21)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	January 2013
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	January 18, 2013
Last Update Posted:	January 24, 2013 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion

CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0
	1	0

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
(Overseas travel - indefinite period)		
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
	Unknown or Not Reported	0 0%	1 1.47%	1 0.58%
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1]	Infiormation retrieved from all baseline participants. Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.		
		104 Participants	68 Participants	172 Participants

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed			
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)

[1] The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)
	[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.			

Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	

	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

	Estimation Parameter	CMH adjusted difference

Method of Estimation	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI

	depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter

		score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

	Comparison Groups	

Statistical Analysis Overview		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53

	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05,

		the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often

	as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

	Estimation Parameter	Difference in LS means

Method of Estimation	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment,

	who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%)	14/97 (14.43%)	7/57 (12.28%)	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104	0/68	0/97	0/57	0/91	0/52

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	52/104 (50%)	44/68 (64.71%)	66/97 (68.04%)	30/57 (52.63%)	38/91 (41.76%)	19/52 (36.54%)
Blood and lymphatic system disorders						
Anaemia [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Eye disorders						
Conjunctival haemorrhage [A*]	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%)	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%)	30/97 (30.93%)	7/57 (12.28%)	17/91 (18.68%)	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%)	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104	7/68	10/97	2/57	0/91	2/52

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Visual acuity reduced [A]	2/104 (1.92%)	7/68 (10.29%)	10/97 (10.31%)	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%)	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%)	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Vascular disorders						
Hypertension [A*]	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: January 25, 2011 (v12)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	January 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	January 25, 2011

Last Update Posted:	January 26, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: January 26, 2012 (v17)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	January 2012
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Certification/Extension First Submitted:	January 26, 2012

Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	January 26, 2012
Last Update Posted:	January 30, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24

3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye

- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: January 30, 2014 (v22)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	January 2014
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	January 30, 2014
Last Update Posted:	March 5, 2014 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	Sponsor
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion

CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of, Gyeonggido

Seongnam-si, Gyeonggido, Korea, Republic of, 463-707

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 137-701

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations: [Study Results] Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, Vitti R, Berliner AJ, Hiemeyer F, Beckmann K, Zeitz O, Sandbrink R. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013 Mar;97(3):278-84. doi: 10.1136/bjophthalmol-2012-301504. Epub 2013 Jan 7.

Erratum in: Br J Ophthalmol. 2015 Dec;99(12):1746. PubMed 23298885

[Study Results] Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, Honda M, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202-208. doi: 10.1016/j.ophtha.2013.08.012. Epub 2013 Sep 29. PubMed 24084497

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0
(Overseas travel - indefinite period)	1	0
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every

	4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age, Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
		0 0%	1 1.47%	1 0.58%

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
	Unknown or Not Reported			
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1] Infiormation retrieved from all baseline participants. Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.			
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)
	[1]	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.		
European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Unit of measure: score on a scale				
	[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.			
Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	CMH adjusted difference
	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit,

	subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value

		indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline

		central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53
	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-

	up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	

		As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05, the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS means
	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and

	depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
	[Not specified]

Adverse Event Reporting Description	

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.
Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week

	60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%)	14/97 (14.43%)	7/57 (12.28%)	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A-]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A-]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A-]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Diverticular perforation [A]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Radius fracture [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	52/104 (50%)	44/68 (64.71%)	66/97 (68.04%)	30/57 (52.63%)	38/91 (41.76%)	19/52 (36.54%)
Blood and lymphatic system disorders						
Anaemia [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Eye disorders						
Conjunctival haemorrhage [A*]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%)	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%)	30/97 (30.93%)	7/57 (12.28%)	17/91 (18.68%)	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%)	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104 (5.77%)	7/68 (10.29%)	10/97 (10.31%)	2/57 (3.51%)	0/91 (0%)	2/52 (3.85%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	2/104 (1.92%)	7/68 (10.29%)	10/97 (10.31%)	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A*]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A*]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A*]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A*]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%)	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A*]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%)	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A*]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A*]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A*]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Vascular disorders						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continue (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Hypertension [A*]	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

Scroll up to access the controls Scroll to the Study top

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: February 9, 2010 (v3)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	February 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	February 9, 2010

Last Update Posted:	February 10, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials:

Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Not yet recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Not yet recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Not yet recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Not yet recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Not yet recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Not yet recruiting]
Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Not yet recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

[Not yet recruiting]
Budapest, Hungary, 1036

[Not yet recruiting]
Budapest, Hungary, 1089

[Not yet recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Not yet recruiting]
Veszprem, Hungary, 8200

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Not yet recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10149

Japan, Aichi

[Not yet recruiting]
Nagoya, Aichi, Japan, 466-8560

[Not yet recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Not yet recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Not yet recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Recruiting]
Ask Contact, Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Not yet recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Not yet recruiting]
Singapore, Singapore, 119074

[Not yet recruiting]
Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: February 20, 2012 (v18)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	February 2012
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Certification/Extension First Submitted:	January 26, 2012

Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	February 20, 2012
Last Update Posted:	February 23, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24

3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye

- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: March 16, 2010 (v4)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19 GALILEO

Study Status

Record Verification:	March 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
	March 16, 2010

Last Update Submitted that Met QC Criteria:	
Last Update Posted:	March 17, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized

Enrollment: 165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact

Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Not yet recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Not yet recruiting]
Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Not yet recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

[Not yet recruiting]
Budapest, Hungary, 1036

[Recruiting]
Budapest, Hungary, 1089

[Recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Not yet recruiting]
Veszprem, Hungary, 8200

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Not yet recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10149

Japan, Aichi

[Recruiting]
Nagoya, Aichi, Japan, 466-8560

[Not yet recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Not yet recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seongsanno, Korea, Republic of

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Not yet recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Recruiting]

Riga, Latvia, LV-1002

Singapore

[Not yet recruiting]

Singapore, Singapore, 119074

[Recruiting]

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: April 8, 2011 (v13)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	April 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	April 8, 2011

Last Update Posted:	April 11, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: April 16, 2010 (v5)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	April 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	April 16, 2010

Last Update Posted:	April 19, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials:

Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Recruiting]
Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

[Recruiting]
Budapest, Hungary, 1036

[Recruiting]
Budapest, Hungary, 1089

[Recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Suspended]
Veszprem, Hungary, 8200

[Not yet recruiting]
Zalaegerszeg, Hungary, 8900

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10149

Japan, Aichi

[Recruiting]
Nagoya, Aichi, Japan, 466-8560

[Recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Recruiting]
ask Contact, Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Recruiting]
Singapore, Singapore, 119074

[Recruiting]
Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: June 23, 2011 (v14)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	June 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	June 23, 2011

Last Update Posted:	June 27, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: July 22, 2010 (v6)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	July 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	July 22, 2010

Last Update Posted:	July 23, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Parramatta, New South Wales, Australia, 2150

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Austria

[Terminated]
Innsbruck, Austria, 6020

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France, Cedex 1

[Recruiting]
Nantes, Cedex 1, France, 44093

France

[Recruiting]
Bordeaux, France, 33000

[Recruiting]
Dijon, France, 21033

[Recruiting]
Marseille, France, 13008

[Recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64297

[Not yet recruiting]
Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

[Recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45122

[Recruiting]
Köln, Nordrhein-Westfalen, Germany, 50924

[Not yet recruiting]
Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Recruiting]
Homburg, Saarland, Germany, 66424

Germany, Sachsen

[Recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Recruiting]
Dresden, Sachsen, Germany, 06067

[Recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Berlin, Germany, 13353

[Recruiting]
Hamburg, Germany, 20251

[Recruiting]
Marburg, Germany, 35037

Hungary

[Recruiting]
Budapest, Hungary, 1036

[Recruiting]
Budapest, Hungary, 1089

[Recruiting]
Budapest, Hungary, 1106

[Recruiting]
Debrecen, Hungary, 4032

[Terminated]
Veszprem, Hungary, 8200

[Not yet recruiting]
Zalaegerszeg, Hungary, H-8900

Italy

[Recruiting]
Ancona, Italy, 60126

[Recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Recruiting]
Firenze, Italy, 50134

[Recruiting]
Milano, Italy, 20122

[Recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Terminated]
Padova, Italy, 35128

[Recruiting]
Roma, Italy, 00133

[Recruiting]
Roma, Italy, 00198

[Not yet recruiting]
Torino, Italy, 10122

Japan, Aichi

[Recruiting]
Nagoya, Aichi, Japan, 466-8560

[Recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Recruiting]
Incheon, Korea, Republic of, 405-760

[Recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Recruiting]
Seoul, Korea, Republic of, 110-744

[Recruiting]
Seoul, Korea, Republic of, 138-736

[Recruiting]
Seoul, Korea, Republic of

Latvia

[Recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Recruiting]
Singapore, Singapore, 119074

[Recruiting]
Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls | Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: August 25, 2010 (v7)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	August 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	August 25, 2010

Last Update Posted:	August 26, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Active, not recruiting]
Chatswood, New South Wales, Australia, 2067

[Active, not recruiting]
Parramatta, New South Wales, Australia, 2150

[Active, not recruiting]
Sydney, New South Wales, Australia, 2000

[Active, not recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Active, not recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Active, not recruiting]
Nedlands, Western Australia, Australia, 6009

Austria

[Terminated]
Innsbruck, Austria, 6020

[Active, not recruiting]
Linz, Austria, 4021

[Active, not recruiting]
Wien, Austria, 1090

France, Cedex 12

[Terminated]
Paris, Cedex 12, France, 75557

France, Cedex 1

[Active, not recruiting]
Nantes, Cedex 1, France, 44093

France

[Active, not recruiting]
Bordeaux, France, 33000

[Active, not recruiting]
Dijon, France, 21033

[Active, not recruiting]
Marseille, France, 13008

[Active, not recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Active, not recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Active, not recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Active, not recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Active, not recruiting]
München, Bayern, Germany, 81675

[Active, not recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Active, not recruiting]
Darmstadt, Hessen, Germany, 64297

[Active, not recruiting]
Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

[Active, not recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Active, not recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Active, not recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Terminated]
Essen, Nordrhein-Westfalen, Germany, 45122

[Active, not recruiting]
Köln, Nordrhein-Westfalen, Germany, 50924

[Terminated]
Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

[Active, not recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Active, not recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Completed]
Homburg, Saarland, Germany, 66424

Germany, Sachsen

[Active, not recruiting]
Chemnitz, Sachsen, Germany, 09116

[Terminated]
Dresden, Sachsen, Germany, 01307

[Active, not recruiting]
Dresden, Sachsen, Germany, 06067

[Active, not recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Active, not recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Active, not recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Terminated]
Berlin, Germany, 13353

[Active, not recruiting]
Hamburg, Germany, 20251

[Active, not recruiting]
Marburg, Germany, 35037

Hungary

[Active, not recruiting]
Budapest, Hungary, 1036

[Active, not recruiting]
Budapest, Hungary, 1089

[Active, not recruiting]
Budapest, Hungary, 1106

[Active, not recruiting]
Debrecen, Hungary, 4032

[Terminated]
Veszprem, Hungary, 8200

[Active, not recruiting]
Zalaegerszeg, Hungary, H-8900

Italy

[Active, not recruiting]
Ancona, Italy, 60126

[Active, not recruiting]
Bari, Italy, 70124

[Terminated]
Catania, Italy, 95123

[Active, not recruiting]
Firenze, Italy, 50134

[Active, not recruiting]
Milano, Italy, 20122

[Active, not recruiting]
Milano, Italy, 20132

[Terminated]
Milano, Italy, 20157

[Terminated]
Padova, Italy, 35128

[Active, not recruiting]
Roma, Italy, 00133

[Active, not recruiting]
Roma, Italy, 00198

[Terminated]
Torino, Italy, 10122

Japan, Aichi

[Active, not recruiting]
Nagoya, Aichi, Japan, 466-8560

[Active, not recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Active, not recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Active, not recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Active, not recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Active, not recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Active, not recruiting]
Incheon, Korea, Republic of, 405-760

[Active, not recruiting]
Kungki-do, Korea, Republic of, 463-707

[Active, not recruiting]
Seoul, Korea, Republic of, 110 744

[Active, not recruiting]
Seoul, Korea, Republic of, 110-744

[Active, not recruiting]
Seoul, Korea, Republic of, 138-736

[Recruiting]
Seoul, Korea, Republic of

Latvia

[Active, not recruiting]
Riga, Latvia, 1009

[Active, not recruiting]
Riga, Latvia, LV-1002

Singapore

[Active, not recruiting]
Singapore, Singapore, 119074

[Active, not recruiting]
Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: August 26, 2010 (v8)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	August 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	August 26, 2010

Last Update Posted:	August 27, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: September 8, 2010 (v9)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	September 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	September 8, 2010

Last Update Posted:	September 9, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: September 19, 2011 (v15)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	September 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	September 19, 2011

Last Update Posted:	September 20, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: October 4, 2010 (v10)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	October 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	October 4, 2010

Last Update Posted:	October 5, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: October 23, 2012 (v19)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	October 2012
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	October 23, 2012
Last Update Posted:	November 22, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	

Macular Edema
Central Retinal Vein Occlusion
CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0
	1	0

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
(Overseas travel - indefinite period)		
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
	Unknown or Not Reported	0 0%	1 1.47%	1 0.58%
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1]	Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.		
	Number Analyzed	104 Participants	68 Participants	172 Participants

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants				
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)

[1] The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.

Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	

	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

	Estimation Parameter	CMH adjusted difference

Method of Estimation	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI

	depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter

		score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

	Comparison Groups	

Statistical Analysis Overview		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53

	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05,

		the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often

	as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

	Estimation Parameter	Difference in LS means

Method of Estimation	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment,

	who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%)	14/97 (14.43%)	7/57 (12.28%)	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104	0/68	0/97	0/57	0/91	0/52

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	52/104 (50%)	44/68 (64.71%)	66/97 (68.04%)	30/57 (52.63%)	38/91 (41.76%)	19/52 (36.54%)
Blood and lymphatic system disorders						
Anaemia [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Eye disorders						
Conjunctival haemorrhage [A*]	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%)	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%)	30/97 (30.93%)	7/57 (12.28%)	17/91 (18.68%)	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%)	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104	7/68	10/97	2/57	0/91	2/52

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Visual acuity reduced [A]	2/104 (1.92%)	7/68 (10.29%)	10/97 (10.31%)	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%)	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%)	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Vascular disorders						
Hypertension [A*]	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: October 27, 2014 (v23)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	October 2014
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	October 27, 2014
Last Update Posted:	November 3, 2014 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	Sponsor
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion

CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68. Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68.

Arms	Assigned Interventions
study retreatment criteria at Week 60 and 68.	

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis

- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of, Gyeonggido

Seongnam-si, Gyeonggido, Korea, Republic of, 463-707

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 137-701

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations: [Study Results] Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, Vitti R, Berliner AJ, Hiemeyer F, Beckmann K, Zeitz O, Sandbrink R. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013 Mar;97(3):278-84. doi: 10.1136/bjophthalmol-2012-301504. Epub 2013 Jan 7.

Erratum in: Br J Ophthalmol. 2015 Dec;99(12):1746. PubMed 23298885

[Study Results] Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, Honda M, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202-208. doi: 10.1016/j.ophtha.2013.08.012. Epub 2013 Sep 29. PubMed 24084497

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5
Lost to Follow-up	1	0
(Overseas travel - indefinite period)	1	0
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every

	4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age, Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
		0 0%	1 1.47%	1 0.58%

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
	Unknown or Not Reported			
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1] Infiormation retrieved from all baseline participants. Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included; a higher score represents better functioning.			
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)
	[1] The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.			
European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Unit of measure: score on a scale				
	[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.			
Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	CMH adjusted difference
	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit,

	subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value

		indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline

		central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53
	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-

	up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	

		As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05, the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS means
	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and

	depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
	[Not specified]

Adverse Event Reporting Description	

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.
Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week

	60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)	Affected/A Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%	14/97 (14.43%	7/57 (12.28%	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A-]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A-]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A-]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						

	Afliberce Injection (Until Week 20)	Sham Treatme (Until Week 20)	Afliberce Injection (Until Week 48)	Sham Treatme (Until Week 48)	Afliberce Injection Continue (Until Week 68)	Sham Treatme Then Afliberce Injection (Until Week 68)
Diverticular perforation [A]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Radius fracture [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A,*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A,*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	52/104 (50%)	44/68 (64.71%)	66/97 (68.04%)	30/57 (52.63%)	38/91 (41.76%)	19/52 (36.54%)
Blood and lymphatic system disorders						
Anaemia [A,*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Eye disorders						
Conjunctival haemorrhage [A,*]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%)	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%)	30/97 (30.93%)	7/57 (12.28%)	17/91 (18.68%)	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%)	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104 (5.77%)	7/68 (10.29%)	10/97 (10.31%)	2/57 (3.51%)	0/91 (0%)	2/52 (3.85%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	2/104 (1.92%)	7/68 (10.29%)	10/97 (10.31%)	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A*]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A*]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A*]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A*]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%)	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A*]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%)	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A*]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A*]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A*]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Vascular disorders						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continue (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Hypertension [A]*	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

Scroll up to access the controls Scroll to the Study top

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: November 1, 2010 (v11)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	November 2010
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	November 1, 2010

Last Update Posted:	November 2, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT)
- Adults >= 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66424

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1036

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1009

Riga, Latvia, LV-1002

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: November 12, 2009 (v1)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19 GALILEO

Study Status

Record Verification:	November 2009
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
	November 12, 2009

Last Update Submitted that Met QC Criteria:	
Last Update Posted:	November 13, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion.
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor

Allocation: Randomized

Enrollment: 165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6.

Change in the EQ-5D score from baseline
Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Not yet recruiting]
Sydney, New South Wales, Australia, 2000

[Not yet recruiting]
Sydney, New South Wales, Australia, 2145

Australia, Victoria

[Not yet recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Not yet recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Not yet recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Not yet recruiting]
Linz, Austria, 4021

[Not yet recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Not yet recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Not yet recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Not yet recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Not yet recruiting]
München, Bayern, Germany, 81675

[Not yet recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Not yet recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Not yet recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Not yet recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Not yet recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Not yet recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Not yet recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Not yet recruiting]
Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Not yet recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Not yet recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

[Not yet recruiting]
Budapest, Hungary, 1036

[Not yet recruiting]
Budapest, Hungary, 1089

[Not yet recruiting]
Budapest, Hungary, 1106

[Not yet recruiting]
Debrecen, Hungary, 4032

[Not yet recruiting]
Veszprem, Hungary, 8200

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Not yet recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10128

Japan, Aichi

[Not yet recruiting]
Nagoya, Aichi, Japan, 466-8560

[Not yet recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Not yet recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Not yet recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Not yet recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of, Korea

[Not yet recruiting]
Seoul, Korea, Korea, Republic of, 110 744

Korea, Republic of

[Not yet recruiting]
Ask Contact, Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Not yet recruiting]
Kungki-do, Korea, Republic of, 463-707

[Not yet recruiting]
Seoul, Korea, Republic of, 110-744

[Not yet recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Not yet recruiting]
Riga, Latvia, LV-1002

Singapore

[Not yet recruiting]
Ask Contact, Singapore, 168751

[Not yet recruiting]
Singapore, Singapore, 119074

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls | Scroll to the Study top

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: November 29, 2011 (v16)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	November 2011
Overall Status:	Active, not recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	March 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	November 29, 2011

Last Update Posted:	November 30, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Biological: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 52 every 4 weeks plus additional on week 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; week 52 VEGF Trap-Eye injection (unless investigator declines for medical reasons), weeks 60 and 68 re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; last visit (no treatment) at week 76.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5.

Change in the NEI-VFQ-25 total score from baseline
Week 24

6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1

- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations:

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Marburg, Germany, 35037

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: December 18, 2012 (v20)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	2009-010973-19 [EudraCT Number]

Study Status

Record Verification:	December 2012
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	February 2011 [Actual]
Study Completion:	February 2012 [Actual]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Results First Submitted:	October 23, 2012
	October 23, 2012

Results First Submitted that Met QC Criteria:	
Results First Posted:	November 22, 2012 [Estimate]
Certification/Extension First Submitted:	January 26, 2012
Certification/Extension First Submitted that Met QC Criteria:	January 26, 2012
Certification/Extension First Posted:	January 30, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	December 18, 2012
Last Update Posted:	December 19, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	

Macular Edema
Central Retinal Vein Occlusion
CRVO
VEGF Trap-Eye
best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	177 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Intravitreal injection. Weeks 0 to 20 of Aflibercept Injection every 4 weeks; Weeks 24 to 52 every 4 weeks PRN (pro re nata, on demand); plus additional on Week 60 and 68.
Sham Comparator: Sham treatment Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept	Sham treatment Sham treatment. Weeks 0 to 52 sham treatment every 4 weeks; plus additional on Week 60 and 68. Biological: Sham treatment switched to Aflibercept Injection

Arms	Assigned Interventions
Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.	Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT)
- Adults ≥ 18 years
- Early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye

Exclusion Criteria:

- Any prior treatment with anti-VEGF agents in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) or previous administration of systemic anti-angiogenic medications
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye

- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

Chatswood, New South Wales, Australia, 2067

Parramatta, New South Wales, Australia, 2150

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Bordeaux, France, 33000

Dijon, France, 21033

Marseille, France, 13008

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Frankfurt, Hessen, Germany, 60596

Marburg, Hessen, Germany, 35037

Germany, Niedersachsen

Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Chemnitz, Sachsen, Germany, 09116

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 13353

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1089

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Debrecen, Hungary, 4032

Veszprem, Hungary, 8200

Zalaegerszeg, Hungary, H-8900

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Firenze, Italy, 50134

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00198

Torino, Italy, 10122

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

Suita, Osaka, Japan, 565-0871

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

Kyoto, Japan, 606-8507

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Kungki-do, Korea, Republic of, 463-707

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 110-744

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1050

Singapore

Singapore, Singapore, 119074

Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Aflibercept Injection First, Then Aflibercept Injection	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment First, Then Aflibercept Injection	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Overall Study

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Started	106	71
Participants Received Treatment	104 [1]	68 [1]
Fulfilled Requirements of FAS Population	103 [2]	68 [2]
Completed Week 24, From FAS	97	57
Completed Week 52, From FAS	91	52
Completed	90	52
Not Completed	16	19
Adverse Event	5	5
Lack of Efficacy	0	5

	Aflibercept Injection First, Then Aflibercept Injection	Sham Treatment First, Then Aflibercept Injection
Lost to Follow-up	1	0
(Overseas travel - indefinite period)	1	0
Increase in vis. acuity, never injected	0	1
Protocol Violation	5	2
Withdrawal by Subject	4	6

[1] Safety Population: Participants received treatment

[2] Full Analysis Set (FAS) Population: Participants received treatment with post baseline measurements

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Baseline Measures

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Overall Number of Participants		104	68	172
Age Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	104 Participants	68 Participants	172 Participants
		60.0 (12.3)	63.8 (13.3)	61.5 (12.8)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Female	45 43.27%	31 45.59%	76 44.19%
	Male	59 56.73%	37 54.41%	96 55.81%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
	Hispanic or Latino	4 3.85%	1 1.47%	5 2.91%
	Not Hispanic or Latino	100 96.15%	66 97.06%	166 96.51%
	Unknown or Not Reported	0 0%	1 1.47%	1 0.58%
Baseline Best Corrected Visual Acuity (BCVA) letter scores [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		53.5 (15.7)	50.9 (15.4)	52.5 (15.6)
	[1]	Only participants with a ETDRS (Early Treatment Diabetic Retinopathy Study) Best Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters were included, Safety Analysis Set (EYLEA n=104, Sham n=68); a higher score represents better functioning.		
		104 Participants	68 Participants	172 Participants

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Number of participants with baseline retinal perfusion [1] Measure type: Number Unit of measure: Participants	Number Analyzed			
Perfused		90	54	144
Nonperfused		7	7	14
Indeterminate		7	7	14
	[1] Retinal perfusion defined as less than 10 disc areas of capillary nonperfusion using fluorescein angiography (FA)			
Baseline Retinal Thickness by Optical Coherence Tomography (OCT) Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		682.78 (233.36)	638.66 (224.69)	665.34 (230.33)
Baseline intraocular pressure Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		15.2 (2.8)	14.4 (2.7)	14.9 (2.8)
Number of participants with time since Central retinal vein occlusion (CRVO) diagnosis Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
>= 2 months		46	33	79
< 2 months		56	35	91
Missing		2	0	2

		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment	Total
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	104 Participants	68 Participants	172 Participants
		79.66 (13.06)	78.94 (14.00)	79.38 (13.40)

[1] The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

European questionnaire 5 dimensions (EQ-5D) total score [1] Mean (Standard Deviation)	Number Analyzed	104 Participants	68 Participants	172 Participants
		0.87 (0.15)	0.86 (0.16)	0.87 (0.15)

[1] The EQ-5D total score ranges from -0.594 to 1.000 with -0.594 being the worst.

Race Measure type: Number Unit of measure: Participants	Number Analyzed	104 Participants	68 Participants	172 Participants
Asian		26	15	41
White		75	49	124
Unknown or Not Reported		3	4	7

Outcome Measures

1. Primary Outcome Measure:

Measure Title	

	Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures
Measure Description	Defined study baseline range of Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. Nominator = (Number of participants who maintained vision * 100); Denominator = Number of participants analyzed.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures Measure Type: Number Unit of Measure: Percentage of participants	60.2	22.1

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 24 With Discontinued Participants Before Week 24 Evaluated as Failures

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis of difference of Eylea minus Sham of 0 was tested. In the database close after Week 24, basis for primary efficacy evaluation, 56 Sham / 96 Eylea subjects were considered as week 24 completers.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

	Estimation Parameter	CMH adjusted difference

Method of Estimation	Estimated Value	38.3
	Confidence Interval	(2-sided) 95% 24.4 to 52.1
	Estimation Comments	The estimate is calculated as Eylea minus Sham. A positive value shows Eylea showed a higher BCVA total score compared to Sham.

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity letter score of 73 to 24 (= Acuity of 20/40 to 20/320) in the study eye; a higher score represents better functioning. However, because this was assessed at the screening visit, subjects may have had a higher BCVA recorded at the baseline visit and would not have been excluded from the study.
Time Frame	Baseline and Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI

	depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: Letters correctly read	71.6 (17.1)	54.3 (20.2)

Statistical Analysis 1 for Change From Baseline in BCVA as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 24 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in BCVA total letter score between Eylea and Sham. If primary efficacy was successful, secondary efficacy endpoints were tested in a pre-specified fixed sequence testing procedure. Change in BCVA letter

		score was to be tested first in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As primary efficacy evaluation was significant, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANOVA
	Comments	ANOVA, adjusting for region and baseline BCVA category as fixed factors.

Method of Estimation	Estimation Parameter	Difference in Least square means
	Estimated Value	14.7
	Confidence Interval	(2-sided) 95% 10.8 to 18.7
	Estimation Comments	The difference is calculated as Eylea minus Sham. A positive value indicates Eylea showed a higher change in BCVA total score until week 24 compared to Sham.

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF
Measure Description	
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	67
Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: microns	-448.58 (256.02)	-169.27 (224.72)

Statistical Analysis 1 for Change From Baseline in Central Retinal Thickness (CRT) at Week 24 - LOCF

	Comparison Groups	

Statistical Analysis Overview		Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Null hypothesis was equality in change from baseline to Week 24 in central retinal thickness between Eylea and Sham. If primary efficacy was successful, secondary efficacy end points were to be tested in a pre-specified fixed sequence testing procedure. Change in central retinal thickness was to be tested at second place in this sequence.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in BCVA until week 24, and this p-value was below significance level of two-sided <.05, the fixed sequence testing did continue with next secondary endpoint.
	Method	ANCOVA
	Comments	ANCOVA, stratified by region and baseline BCVA category, baseline central retinal thickness added as covariate.

Method of Estimation	Estimation Parameter	Difference in Least square (LS) means
	Estimated Value	-239.42
	Confidence Interval	(2-sided) 95% -286.31 to -192.53

	Estimation Comments	The difference is calculated as Eylea minus Sham. A negative value indicates Eylea showed a higher reduction in change in central retinal thickness until week 24 compared to Sham.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed Neovascularization During the First 24 Weeks
Measure Description	Formation of blood vessels in the anterior segment, optic disc, or elsewhere in the fundus up to Week 24
Time Frame	From baseline until Week 24

Analysis Population Description

Full analysis set

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	103	68
Percentage of Participants Who Developed Neovascularization During the First 24 Weeks Measure Type: Number Unit of Measure: Percentage of participants		
Any neovascularization	2.9	4.4
Anterior segment neovascularization	1.9	1.5
Neovascularization of the optic disc (NVD)	0.0	0.0
Neovascularization elsewhere in the fundus (NVE)	1.0	2.9

Statistical Analysis 1 for Percentage of Participants Who Developed Neovascularization During the First 24 Weeks

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	Nullhypothesis of no difference in development of neovascularizations between Eylea and Sham group was tested. (Any neovascularization)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5947
	Comments	As fixed sequence testing did reject nullhypothesis of change from baseline in CRT until week 24, and this p-value was not below significance level of two-sided <.05,

		the fixed sequence testing did end with this evaluation.
	Method	Cochran-Mantel-Haenszel
	Comments	Cochrane-Mantel-Haenszel test, stratified by region and baseline BCVA category.

Method of Estimation	Estimation Parameter	CMH adjusted Difference
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95% -7.4 to 4.4
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often

	as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment, who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	96	65
Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	7.46 (9.55)	3.55 (9.74)

Statistical Analysis 1 for Change From Baseline in National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) Total Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

	Estimation Parameter	Difference in LS means

Method of Estimation	Estimated Value	4.2
	Confidence Interval	(2-sided) 95% 1.7 to 6.8
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF
Measure Description	EQ-5D is a quality of life questionnaire based on a scale from -0.594 (worst) to 1.00 (best).
Time Frame	Baseline and Week 24

Analysis Population Description

Full-Analysis Set with assessment for this outcome measure; imputation technique: LOCF

Reporting Groups

	Description
Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20, later as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Follow-up phase: Participants on IAI, who continued the study, received 2 mg dose of IAI depending on the study retreatment criteria at Week 60 and 68.
Sham Treatment	Participants received sham treatment administered every 4 weeks from Day 1 through Week 52. Follow-up phase: Participants on sham treatment,

	who switched to Intravitreal Aflibercept Injection (IAI), received a 2 mg dose of IAI at week 52 and depending on the study retreatment criteria at Week 60 and 68.

Measured Values

	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321)	Sham Treatment
Overall Number of Participants Analyzed	95	64
Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: Scores on a scale	0.029 (0.139)	-0.002 (0.195)

Statistical Analysis 1 for Change From Baseline in European Five-dimensional Health Scale (EQ-5D) Score at Week 24 - LOCF

Statistical Analysis Overview	Comparison Groups	Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321), Sham Treatment
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Difference in LS Means
	Estimated Value	0.044
	Confidence Interval	(2-sided) 95% -0.002 to 0.09
	Estimation Comments	As the fixed sequence of secondary endpoints stopped with proportion of neovascularizations developed until week 24, 95% confidence interval is only of descriptive nature.

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Aflibercept Injection (Until Week 20)	Participants received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Sham Treatment (Until Week 20)	Participants received sham treatment administered every 4 weeks from Day 1 through Week 20. Participants were observed until Week 24. Participants in the safety population were at risk.
Aflibercept Injection (Until Week 48)	Participants who continued the study drug until Week 24 received a 2 mg dose of Intravitreal Aflibercept Injection (IAI) administered as often as every 4 weeks depending on the study retreatment criteria from Week 24 through Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Sham Treatment (Until Week 48)	Participants who continued the study drug until Week 24 received sham treatment administered every 4 weeks from Week 24 to Week 48. Participants were observed from Week 24 until Week 52. Participants in the safety population that completed Week 24 were at risk.
Aflibercept Injection Continued (Until Week 68)	Participants on IAI who continued the study drug until Week 52, received 2 mg dose of IAI depending on the study retreatment criteria at Week 52, 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

Sham Treatment Then Aflibercept Injection (Until Week 68)	Participants on sham treatment switched to IAI, received a 2 mg dose of IAI at Week 52 and depending on the study retreatment criteria at Week 60 and 68. Participants were observed starting from Week 52. Participants in the safety population that completed Week 52 were at risk.

All-Cause Mortality

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/104 (7.69%)	8/68 (11.76%)	14/97 (14.43%)	7/57 (12.28%)	4/91 (4.4%)	3/52 (5.77%)
Cardiac disorders						
Aortic valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Cardiac failure [A*]						

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Coronary artery stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Diastolic dysfunction [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Mitral valve incompetence [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Eye disorders						
Blindness unilateral [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Glaucoma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Iris neovascularisation [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular fibrosis [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular ischaemia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Macular oedema [A*]	0/104 (0%)	2/68 (2.94%)	4/97 (4.12%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Retinal vein occlusion [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Visual acuity reduced [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	2/91 (2.2%)	0/52 (0%)
Vitreous detachment [A*]	1/104	0/68	0/97	0/57	0/91	0/52

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Vitreous haemorrhage [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Gastrointestinal disorders						
Diverticular perforation [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Hepatobiliary disorders						
Hepatic function abnormal [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Furuncle [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Gastroenteritis [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Pneumonia [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Vestibular neuronitis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Injury, poisoning and procedural complications						
Fall [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Femur fracture [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Hand fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Humerus fracture [A*]	0/104 (0%)	1/68 (1.47%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Radius fracture [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal compression fracture [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Spinal column stenosis [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Oropharyngeal cancer stage unspecified [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Nervous system disorders						
Paraesthesia [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Syncope [A*]	0/104 (0%)	0/68 (0%)	1/97 (1.03%)	2/57 (3.51%)	0/91 (0%)	0/52 (0%)
Transient ischaemic attack [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	1/57 (1.75%)	0/91 (0%)	0/52 (0%)
Laryngeal granuloma [A*]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Pulmonary hypertension [A*]	0/104 (0%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	1/52 (1.92%)
Surgical and medical procedures						
Ischaemic heart disease prophylaxis [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vascular disorders						
Circulatory collapse [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	0/57 (0%)	0/91 (0%)	0/52 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	52/104 (50%)	44/68 (64.71%)	66/97 (68.04%)	30/57 (52.63%)	38/91 (41.76%)	19/52 (36.54%)
Blood and lymphatic system disorders						
Anaemia [A*]	1/104 (0.96%)	0/68 (0%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Eye disorders						
Conjunctival haemorrhage [A*]	10/104 (9.62%)	3/68 (4.41%)	3/97 (3.09%)	0/57 (0%)	9/91 (9.89%)	3/52 (5.77%)
Eye irritation [A*]	3/104 (2.88%)	7/68 (10.29%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	2/52 (3.85%)
Eye pain [A*]	12/104 (11.54%)	3/68 (4.41%)	6/97 (6.19%)	2/57 (3.51%)	1/91 (1.1%)	0/52 (0%)
Foreign body sensation in eyes [A*]	6/104 (5.77%)	5/68 (7.35%)	2/97 (2.06%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Lacrimation increased [A*]	3/104 (2.88%)	4/68 (5.88%)	3/97 (3.09%)	4/57 (7.02%)	1/91 (1.1%)	2/52 (3.85%)
Macular fibrosis [A*]	1/104 (0.96%)	1/68 (1.47%)	5/97 (5.15%)	4/57 (7.02%)	0/91 (0%)	3/52 (5.77%)
Macular ischaemia [A*]	7/104 (6.73%)	5/68 (7.35%)	3/97 (3.09%)	1/57 (1.75%)	0/91 (0%)	1/52 (1.92%)
Macular oedema [A*]	2/104 (1.92%)	9/68 (13.24%)	30/97 (30.93%)	7/57 (12.28%)	17/91 (18.68%)	2/52 (3.85%)
Ocular hyperaemia [A*]	5/104 (4.81%)	4/68 (5.88%)	2/97 (2.06%)	1/57 (1.75%)	4/91 (4.4%)	1/52 (1.92%)
Optic disc vascular disorder [A*]	5/104 (4.81%)	3/68 (4.41%)	3/97 (3.09%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal exudates [A*]	8/104 (7.69%)	5/68 (7.35%)	4/97 (4.12%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Retinal haemorrhage [A*]	4/104 (3.85%)	6/68 (8.82%)	11/97 (11.34%)	5/57 (8.77%)	5/91 (5.49%)	2/52 (3.85%)
Retinal vascular disorder [A*]	6/104	7/68	10/97	2/57	0/91	2/52

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Visual acuity reduced [A]	2/104 (1.92%)	7/68 (10.29%)	10/97 (10.31%)	1/57 (1.75%)	7/91 (7.69%)	1/52 (1.92%)
Vitreous detachment [A]	2/104 (1.92%)	1/68 (1.47%)	7/97 (7.22%)	0/57 (0%)	0/91 (0%)	0/52 (0%)
Vitreous floaters [A]	6/104 (5.77%)	0/68 (0%)	1/97 (1.03%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Gastrointestinal disorders						
Nausea [A]	0/104 (0%)	1/68 (1.47%)	0/97 (0%)	3/57 (5.26%)	0/91 (0%)	0/52 (0%)
Infections and infestations						
Influenza [A]	2/104 (1.92%)	0/68 (0%)	5/97 (5.15%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)
Nasopharyngitis [A]	8/104 (7.69%)	6/68 (8.82%)	10/97 (10.31%)	11/57 (19.3%)	4/91 (4.4%)	2/52 (3.85%)
Investigations						
Intraocular pressure increased [A]	9/104 (8.65%)	4/68 (5.88%)	14/97 (14.43%)	2/57 (3.51%)	2/91 (2.2%)	1/52 (1.92%)
Visual acuity tests abnormal [A]	0/104 (0%)	1/68 (1.47%)	5/97 (5.15%)	0/57 (0%)	1/91 (1.1%)	0/52 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A]	1/104 (0.96%)	5/68 (7.35%)	2/97 (2.06%)	1/57 (1.75%)	2/91 (2.2%)	0/52 (0%)
Nervous system disorders						
Headache [A]	7/104 (6.73%)	4/68 (5.88%)	4/97 (4.12%)	1/57 (1.75%)	1/91 (1.1%)	1/52 (1.92%)

	Aflibercept Injection (Until Week 20)	Sham Treatment (Until Week 20)	Aflibercept Injection (Until Week 48)	Sham Treatment (Until Week 48)	Aflibercept Injection Continued (Until Week 68)	Sham Treatment Then Aflibercept Injection (Until Week 68)
Vascular disorders						
Hypertension [A*]	4/104 (3.85%)	3/68 (4.41%)	4/97 (4.12%)	4/57 (7.02%)	3/91 (3.3%)	2/52 (3.85%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publishing of result communication only after Bayer´s written approval. Manuscript to Bayer sixty days before public release. If no written Bayer comment within 60 days consider approval given. If multi-site study, principal investigator (PI) not do independently publish results before publication of the multi-site paper, but PI not restricted from 24 months from study to completion onwards.

Results Point of Contact:

Name/Official Title: Therapeutic Area Head
Organization: BAYER
Phone:
Email: clinical-trials-contact@bayerhealthcare.com

History of Changes for Study: NCT01012973

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)

Latest version (submitted October 27, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's date link to see a rendering of the study for that version.
- Edits or deletions will be displayed in ~~red~~.
- Additions will be displayed in *green*.
- The yellow choices in the table indicate the study versions currently compared below. A yellow row indicates the study version being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	○	November 12, 2009	Nothing (earliest Version on record)
2	○	○	January 21, 2010	Contacts/Locations, Study Status, Study Identification and Study Description
3	○	○	February 9, 2010	Contacts/Locations and Study Status
4	○	○	March 16, 2010	Contacts/Locations, Study Status and Study Identification
5	○	○	April 16, 2010	Contacts/Locations, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
6	○	○	July 22, 2010	Contacts/Locations, Study Status, Eligibility and Arms and Interventions
7	○	○	August 25, 2010	Study Status and Contacts/Locations
8	○	○	August 26, 2010	Recruitment Status, Study Status and Contacts/Locations
9	○	○	September 8, 2010	Study Status
10	○	○	October 4, 2010	Study Status
11	○	○	November 1, 2010	Study Status
12	○	○	January 25, 2011	Study Status and Contacts/Locations
13	○	○	April 8, 2011	Study Status and Study Design
14	○	○	June 23, 2011	Arms and Interventions, Study Status, Contacts/Locations and Eligibility
15	○	○	September 19, 2011	Study Status
16	○	○	November 29, 2011	Study Status and Study Identification
17	○	○	January 26, 2012	Study Status and Contacts/Locations
18	○	○	February 20, 2012	Recruitment Status, Study Status
19	○	○	October 23, 2012	Outcome Measures, Arms and Interventions, Study Status, More Information, Reported Adverse Events, Baseline Characteristics and Participant Flow
20	○	○	December 18, 2012	More Information, Arms and Interventions, Study Status and Baseline Characteristics
21	○	○	January 18, 2013	Arms and Interventions, More Information, Study Status and Baseline Characteristics
22	○	○	January 30, 2014	Contacts/Locations, Sponsor/Collaborators, More Information, Study Status, Baseline Characteristics and References
23	○	◉	October 27, 2014	More Information, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT01012973
on Date: January 21, 2010 (v2)

Study Identification

Unique Protocol ID:	14130
Brief Title:	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO)
Official Title:	A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)
Secondary IDs:	EudraCT: 2009-010973-19

Study Status

Record Verification:	January 2010
Overall Status:	Recruiting
Study Start:	October 2009
Primary Completion:	February 2011 [Anticipated]
Study Completion:	August 2012 [Anticipated]
First Submitted:	October 30, 2009
First Submitted that Met QC Criteria:	November 12, 2009
First Posted:	November 13, 2009 [Estimate]
Last Update Submitted that Met QC Criteria:	January 21, 2010

Last Update Posted:	January 22, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	To determine the efficacy of vascular endothelial growth factor (VEGF) Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion
Detailed Description:	

Conditions

Conditions:	Retinal Vein Occlusion
Keywords:	Macular Edema Central Retinal Vein Occlusion CRVO VEGF Trap-Eye best-corrected visual acuity

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	TripleParticipant, Investigator, Outcomes Assessor
Allocation:	Randomized
Enrollment:	165 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Arm 1	Drug: VEGF Trap-Eye (BAY86-5321) Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up.
Sham Comparator: Arm 2	Sham treatment Sham treatment. Weeks 0 to 20 sham treatment every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who gain at least 15 letters in BCVA on the EDTRS chart compared with baseline at the Week 24 endpoint
   Week 24

Secondary Outcome Measures:

2. Change from baseline in BCVA score
   Week 24
3. Absolute change from baseline in central retinal thickness, assessed by OCT
   Week 24
4. Proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation
   Week 24
5. Change in the NEI-VFQ-25 total score from baseline
   Week 24
6. Change in the EQ-5D score from baseline
   Week 24

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Center-involved macular edema secondary to central retinal vein occlusion (CRVO) for no longer than 9 months with mean central subfield thickness >= 250 µm on optical coherence tomography (OCT).
- Adults >= 18 years.
- early treatment diabetic retinopathy study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Exclusion Criteria:

- Previous treatment with anti-angiogenic drugs in the study eye (Pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.)
- Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye
- CRVO disease duration > 9 months from date of diagnosis
- Previous use of intraocular corticosteroids in the study eye or use of periocular corticosteroids in the study eye within the 3 months prior to Day 1
- Iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or fellow eye

Contacts/Locations

Central Contact: Bayer Clinical Trials Contact
Email: clinical-trials-contact@bayerhealthcare.com

Study Officials:

Bayer Study Director
Study Director
Bayer

Locations: **Australia, New South Wales**

[Not yet recruiting]
Chatswood, New South Wales, Australia, 2067

[Recruiting]
Sydney, New South Wales, Australia, 2000

[Not yet recruiting]
Westmead, New South Wales, Australia, 2145

Australia, Victoria

[Recruiting]
East Melbourne, Victoria, Australia, 3002

Australia, Western Australia

[Recruiting]
Nedlands, Western Australia, Australia, 6009

Australia

[Recruiting]
Parramatta, Australia, 2150

Austria, Oberösterreich

[Not yet recruiting]
Linz, Oberösterreich, Austria, 4020

Austria, Tirol

[Not yet recruiting]
Innsbruck, Tirol, Austria, 6020

Austria

[Recruiting]
Linz, Austria, 4021

[Recruiting]
Wien, Austria, 1090

France, Cedex 12

[Not yet recruiting]
Paris, Cedex 12, France, 75557

France

[Not yet recruiting]
Bordeaux, France, 33000

[Not yet recruiting]
Dijon Cedex, France, BP 1542-21

[Not yet recruiting]
Marseille, France, 13008

[Not yet recruiting]
Nantes Cedex, France, 44035

[Not yet recruiting]
Paris, France, 75015

Germany, Baden-Württemberg

[Not yet recruiting]
Freiburg, Baden-Württemberg, Germany, 79106

[Not yet recruiting]
Heidelberg, Baden-Württemberg, Germany, 69120

[Recruiting]
Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

[Recruiting]
München, Bayern, Germany, 81675

[Recruiting]
Regensburg, Bayern, Germany, 93053

Germany, Hessen

[Recruiting]
Darmstadt, Hessen, Germany, 64276

[Not yet recruiting]
Marburg, Hessen, Germany, 35043

Germany, Niedersachsen

[Not yet recruiting]
Göttingen, Niedersachsen, Germany, 37075

Germany, Nordrhein-Westfalen

[Not yet recruiting]
Aachen, Nordrhein-Westfalen, Germany, 52074

[Recruiting]
Bonn, Nordrhein-Westfalen, Germany, 53105

[Not yet recruiting]
Essen, Nordrhein-Westfalen, Germany, 45147

[Not yet recruiting]
Köln, Nordrhein-Westfalen, Germany, 50931

Germany, Rheinland-Pfalz

[Recruiting]
Ludwigshafen, Rheinland-Pfalz, Germany, 67063

[Recruiting]
Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

[Not yet recruiting]
Homburg, Saarland, Germany, 66421

Germany, Sachsen

[Not yet recruiting]
Chemnitz, Sachsen, Germany, 09116

[Not yet recruiting]
Dresden, Sachsen, Germany, 01067

[Not yet recruiting]
Dresden, Sachsen, Germany, 01307

[Not yet recruiting]
Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

[Not yet recruiting]
Kiel, Schleswig-Holstein, Germany, 24105

[Not yet recruiting]
Lübeck, Schleswig-Holstein, Germany, 23538

Germany

[Not yet recruiting]
Hamburg, Germany, 20251

Hungary

[Not yet recruiting]
Budapest, Hungary, 1036

[Not yet recruiting]
Budapest, Hungary, 1089

[Not yet recruiting]
Budapest, Hungary, 1106

[Not yet recruiting]
Debrecen, Hungary, 4032

[Not yet recruiting]
Veszprem, Hungary, 8200

Italy

[Not yet recruiting]
Ancona, Italy, 60126

[Not yet recruiting]
Bari, Italy, 70124

[Not yet recruiting]
Catania, Italy, 95123

[Not yet recruiting]
Firenze, Italy, 50139

[Not yet recruiting]
Milano, Italy, 20122

[Not yet recruiting]
Milano, Italy, 20132

[Not yet recruiting]
Milano, Italy, 20157

[Not yet recruiting]
Padova, Italy, 35128

[Not yet recruiting]
Roma, Italy, 00133

[Not yet recruiting]
Roma, Italy, 00185

[Not yet recruiting]
Torino, Italy, 10128

Japan, Aichi

[Not yet recruiting]
Nagoya, Aichi, Japan, 466-8560

[Not yet recruiting]
Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

[Recruiting]
Urayasu, Chiba, Japan, 279-0021

Japan, Osaka

[Not yet recruiting]
Suita, Osaka, Japan, 565-0871

Japan, Tokyo

[Not yet recruiting]
Chiyoda-ku, Tokyo, Japan, 101-8309

Japan

[Not yet recruiting]
Kyoto, Japan, 606-8507

Korea, Republic of

[Not yet recruiting]
Ask Contact, Korea, Republic of

[Not yet recruiting]
Incheon, Korea, Republic of, 405-760

[Not yet recruiting]
Kungki-do, Korea, Republic of, 463-707

[Recruiting]
Seoul, Korea, Republic of, 110 744

[Not yet recruiting]
Seoul, Korea, Republic of, 110-744

[Not yet recruiting]
Seoul, Korea, Republic of, 138-736

Latvia

[Not yet recruiting]
Riga, Latvia, 1009

[Recruiting]
Riga, Latvia, LV-1002

Singapore

[Not yet recruiting]
Singapore, Singapore, 119074

[Not yet recruiting]
Singapore, Singapore, 168751

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls | Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

Electronic Patent Application Fee Transmittal

Application Number:	16055847
Filing Date:	06-Aug-2018
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON3

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	38657627
Application Number:	16055847
International Application Number:	
Confirmation Number:	3451
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON3
Receipt Date:	21-FEB-2020
Filing Date:	06-AUG-2018
Time Stamp:	15:14:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	E20202KF14431490
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	0725US04_2020-02-20_Supp_IDS_trans_REGN-008CIPCON3.pdf	50753 6ddeef26634d417fc64ceffa13e3d523641a5161	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	0725US04__2020-02-20_Supp_IDS_SB08A.pdf	42085 df3eec6fc101792117 4db59ab22d289837e35444	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	NCT01012973_01182013_27424_1a.pdf	387850 3611596cbf2c3151497ab7f1023827335e74dfd0	no	38
Warnings:					
Information:					
4	Non Patent Literature	NCT01012973_01252011_27433_1a.pdf	202886 863ea430a0b1a1cd4db6546121ce51493c626a14	no	10
Warnings:					
Information:					
5	Non Patent Literature	NCT01012973_01262012_27428_1a.pdf	204978 9da69fc33b0b54b02ac3a5bc75335ad9b67f02a0	no	11
Warnings:					
Information:					
6	Non Patent Literature	NCT01012973_01302013_27423_1a.pdf	393002 e94c0f2f9b72f0c70de9124d70f494ad9963edb0	no	38
Warnings:					

Information:					
7	Non Patent Literature	NCT01012973_02092010_27442_1a.pdf	205517 146573f030447d3e752726652930460f5a8e115	no	12
Warnings:					
Information:					
8	Non Patent Literature	NCT01012973_02202012_27427_1a.pdf	205076 0b34980c7a0f3e5e341d6b0c58b7346829ae9b16	no	11
Warnings:					
Information:					
9	Non Patent Literature	NCT01012973_03162010_27441_1a.pdf	205838 0b335c9cac34627988ae78c5fadd06e351e30197	no	12
Warnings:					
Information:					
10	Non Patent Literature	NCT01012973_04082011_27432_1a.pdf	202854 2b6eaff33edab7147db38435285f46f2b6befc80	no	10
Warnings:					
Information:					
11	Non Patent Literature	NCT01012973_04162010_27440_1a.pdf	206353 115b4761e50f4e965b2b6bf7a18f495e2e3732bd	no	12
Warnings:					
Information:					
12	Non Patent Literature	NCT01012973_06232011_27431_1a.pdf	202913 73584750b04b8b43d9c186c24e32a6a739d61557	no	10
Warnings:					
Information:					
13	Non Patent Literature	NCT01012973_07222010_27439_1a.pdf	206587 945460bfe03ce65f025e72290b2a2aa0ec6e18dd	no	12
Warnings:					
Information:					

14	Non Patent Literature	NCT01012973_08252010_27438_1a.pdf	207066 582fe282007a1d7a122b245830b5a0cef56595e9	no	12
Warnings:					
Information:					
15	Non Patent Literature	NCT01012973_08262010_27437_1a.pdf	203139 fa7f94b3e8de7bb3ef65f3adac4d9145c4736123	no	10
Warnings:					
Information:					
16	Non Patent Literature	NCT01012973_09082010_27436_1a.pdf	202787 10f24e5ee4809b91556b3959a04af8002920bbf1	no	10
Warnings:					
Information:					
17	Non Patent Literature	NCT01012973_09192011_27430_1a.pdf	202833 f8c01baf26e9d562dae1246e3590022a470d2e8e	no	10
Warnings:					
Information:					
18	Non Patent Literature	NCT01012973_10042010_27435_1a.pdf	202793 947ae692be386b88631fedf064a2933898a81924	no	10
Warnings:					
Information:					
19	Non Patent Literature	NCT01012973_10232012_27426_1a.pdf	387280 baa1f57c36ac7107700b3484197711e18792a8c9	no	38
Warnings:					
Information:					
20	Non Patent Literature	NCT01012973_10272013_27422_1a.pdf	393007 96988a4c0bc0506e694fab39a1198e4a2bcce693	no	38
Warnings:					
Information:					

21	Non Patent Literature	NCT01012973_11012010_27434_1a.pdf	202609 419a169b77875f93570ffb485e599399b6d350d5	no	10
Warnings:					
Information:					
22	Non Patent Literature	NCT01012973_11132009_27444_1a.pdf	205352 2014c1892ab17afd7ae36889f0cbf4f35d3a8e28	no	12
Warnings:					
Information:					
23	Non Patent Literature	NCT01012973_11292011_27429_1a.pdf	202738 1e20bf11575dd80b56a6cc6d51744682dc430bd4	no	10
Warnings:					
Information:					
24	Non Patent Literature	NCT01012973_12182012_27425_1a.pdf	387906 1b275ad8ebcdd13b7008bbb387c8d249babeabd7	no	38
Warnings:					
Information:					
25	Non Patent Literature	NCT01012973_12212010_27443_1a.pdf	205393 69eca39829ebf95d6eadd663cc3719a86ca210b9	no	12
Warnings:					
Information:					
26	Fee Worksheet (SB06)	fee-info.pdf	30915 4d862bf7cbf125addff55503982fd43f505cd57e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5750510		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON3
	Confirmation No.	3451
	First Named Inventor	George D. Yancopoulos
	Application Number	16/055,847
	Filing Date	August 6, 2018
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON3.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 20 February 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Electronically filed 3/12/2020		
INTERVIEW SUMMARY	Attorney Docket No.	REGN-008CIPCON3
	Confirmation No.	3451
	First Named Inventor	George D. Yancopoulos
	Application Number	16/055,847
Address to: Mail Stop AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Filing Date	August 6, 2018
	Group Art Unit	1647
	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This Interview Summary documents the Examiner initiated telephone interview of March 6, 2020.

Examiner Lockard called the undersigned to discuss the response filed by the undersigned on January 23, 2020.

The pending claims begin on page 2 of this document.

Remarks and summary of the interview begin on page 3 of this document.

AMENDMENTS TO THE CLAIMS

1. - 20. (**Canceled**)

21. (**Previously Presented**) A method for treating macular edema following retinal vein occlusion in a human subject comprising administering 2 mg aflibercept to the subject by intravitreal injection once every 4 weeks.

22. (**Previously Presented**) The method of claim 21 wherein the aflibercept is administered in a volume of 0.05 ml.

23. (**Previously Presented**) The method of claim 22 wherein the aflibercept is in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier.

REMARKS

Formal Matters

Claims 21-23 are now pending in this application.

Claims 1-20 were previously canceled without prejudice.

No new matter has been added.

Interview Summary

Examiner Lockard called the undersigned to discuss the priority date with respect to the "clinical trial" document indicated as being published on November 13, 2009.

The matter was discussed with the client by phone on March 9, 2020. As stated in our Office Action Response, it is applicant's belief that the "clinical trial" reference cited in support of the rejection was not published on November 13, 2009. Applicant has reviewed each of the updates to trial NCT01012973 that clinicaltrials.gov identified as having a date between November 13, 2009 and January 11, 2012 and has provided this trial's updates in an IDS for the Examiner's independent review and consideration. Based on its review, Applicant can confirm that none of the clinicaltrials.gov updates identified as having dates on or before January 11, 2012 disclosed the recited 2 mg dosing regimen. Consequently, Applicant respectfully submits that the 2 mg dosing regimen is novel over the prior art of record.

Since every element of the claimed method was not disclosed before the priority dates, the claims are novel over the clinical trial reference. Accordingly, as explained in the response filed on January 23, 2020, the rejection should be reconsidered and withdrawn.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No.

14/972,560, filed December 17, 2015 which issued on June 6, 2018 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,691.

The Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,282, filed October 12, 2018 for which a response to non-final Office Action was filed on January 23, 2020.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON3.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 12, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Electronic Acknowledgement Receipt

EFS ID:	38851763
Application Number:	16055847
International Application Number:	
Confirmation Number:	3451
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON3
Receipt Date:	12-MAR-2020
Filing Date:	06-AUG-2018
Time Stamp:	17:07:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	REGN-008CIPCON3_2020-03-12_Interview_Summary.pdf	36541 a6f1f4b5322615937a256bbb332c92de752cde30	no	5

Warnings:

Information:	
Total Files Size (in bytes):	36541

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

96387 7590 04/01/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/01/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/055,847	08/06/2018	George D. Yancopoulos	REGN-008CIPCON3	3451

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	07/01/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

96387 7590 04/01/2020
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/055,847	08/06/2018	George D. Yancopoulos	REGN-008CIPCON3	3451

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	07/01/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/055,847	08/06/2018	George D. Yancopoulos	REGN-008CIPCON3	3451

96387 7590 04/01/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/01/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/055,847	Applicant(s) Yancopoulos, George D.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Response filed 23 January 2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 21-23 (renumbered as claims 1-3, respectively) . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 20200324.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on 23 January 2020, 27 January 2020 and 21 February 2020 have been considered by the examiner.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

3. The Response filed 23 January 2020 has been received and entered in full. Claims 21-23 are pending and the subject of this Office Action.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

5. The rejection of claims 21 and 23 under pre-AIA 35 U.S.C. 102(b) as set forth at pp. 2-3 of the previous Office action (mailed 10 December 2019) is withdrawn after further consideration in response to Applicant's persuasive arguments as they pertain to the publication date of the "Clinical Trial" reference cited in the rejection. None of the published clinicaltrials.gov updates having dates on before January 11, 2012 disclose the dosing regimen recited in the instant claims.

6. The rejection of claim 22 under pre-AIA 35 U.S.C. 103(a) as set forth at pp. 3-5 of the previous Office action (mailed 10 December 2019) is withdrawn after further consideration in response to Applicant's persuasive arguments as they pertain to the publication date of the

"Clinical Trial" reference cited in the rejection. None of the published clinicaltrials.gov updates having dates on before January 11, 2012 disclose or fairly suggest the dosing regimen recited in the instant claims.

Summary

7. Claims 21-23 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647

/J.L/
Examiner, Art Unit 1647
March 25, 2020

Examiner-Initiated Interview Summary	**Application No.** 16/055,847	**Applicant(s)** Yancopoulos, George D.	
	Examiner JON M LOCKARD	**Art Unit** 1647	**AIA (FITF) Status** No

All participants (applicant, applicant's representative, PTO personnel):

(1) JON M. LOCKARD. (3) _____.

(2) KARL BOZICEVIC. (4) _____.

Date of Interview: 06 March 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☑ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 21-23.

Identification of prior art discussed: Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO), i.e., "Clinical Trial"..

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The Examiner called to discuss the priority date with respect to the "Clinical Trial" reference which served as the basis for the rejections under 35 U.S.C. 102 and 103. An agreement was not reached..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JON M LOCKARD/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/055,847	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	179	F	2013-01-01
C07K	/	16	/	22	I	2013-01-01
C07K	/	14	/	71	I	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2319	/	32	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/JON M LOCKARD/ Examiner, Art Unit 1647	25 March 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	27 March 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200324

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/055,847	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
A61K	/	38	/	18	
C07K	/	14	/	71	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JON M LOCKARD/ Examiner, Art Unit 1647	25 March 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	27 March 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/055,847	Yancopoulos, George D.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JON M LOCKARD/ Examiner, Art Unit 1647	25 March 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	27 March 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20200324

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/055,847	Yancopoulos, George D.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		12/05/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	12/05/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	12/05/2019	JML
PALM: Inventor search.	12/05/2019	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	EAST (USPAT): See attached search history.	03/24/2020	JML
	PALM: Inventor search.	03/24/2020	JML

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	16/159,282 – Third Party Submissions dated May 31, 2019	
	2	BROWN, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 120(10):2013-22 (October 2013)	
	3	CAMPOCHIARO, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion: six-month primary end point results of a phase III study." Ophthalmology, 117(6):1102-1112 (June 2010)	
	4	DIXON et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" Expert Opin. Investig. Drugs, 18(10):1573-1580 (2009)	
	5	DO, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 119(8):1658-65 (2012)	
	6	ENGELBERT, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, Issue 42, (June 2010) available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42	
	7	GOMEZ-MANZANO, "VEGF Trap induces antiglioma effect at different stages of disease." Neuro-Oncology, 10:940-945 (December 2008)	
	8	HEIER, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies." Ophthalmology, 123(11):2376-2385 (November 2016)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973) (NOTE: May correspond to "Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]**" which was cited in the Third Party Observations dated 05/01/19)	
	10	KAISER, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema." Br. J. Ophthalmol, 93(2):135-36 (February 2009)	
	11	MARGOLIS, "Hemorrhagic Recurrence Of Neovascular Age-Related Macular Degeneration Not Predicted By Spectral Domain Optical Coherence Tomography." Retinal Cases & Brief Reports, 4:1-4 (2010)	
	12	NICHOLS, EARL R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (November 24, 2003)	
	13	SCHMIDT-ERFURTH, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCIE Study" Ophthalmology, 118(5)831-839 (2010)	
	14	SCHNICHELS, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." Br. J. Ophthalmol., 97:917-923 (2013)	
	15	SIMO AND HERNANDEZ, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, 32(8):1556-1562 (August 2009)	
	16	SPAIDE, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." Am J Ophthalmology, 143(4):679-680 (April 2007)	
	17	Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and Safety in Central Retinal Vein Occlusion title, 8 pages, 11/12/2009, US **[Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR] NOTE:** May correspond to **"**Information from ClinicalTrials.gov archive on the view of NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted 11/13/2009; results first posted 11/22/2012; last update posted 11/3/14; printed 12/4/19 (https://clinicaltrials.gov/ct2/show/study/NCT01012973)" cited by the Examiner in the Office Action dated 12/10/19 in USSN 16/055,847	
	18	YANCOPOULOS, "Clinical Application of Therapies Targeting VEGF." Cell 143:13-16 (October 1, 2010)	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/24/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	4	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				
	2				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01182013_27424.1)	
	2	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01252011_27433.1)	
	3	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01262012_27428.1)	
	4	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01302013_27423.1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	4	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	5	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02092010_27442.1)	
	6	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 11 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_02202012_27427.1)	
	7	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_03162010_27441.1)	
	8	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04082011_27432.1)	
	9	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_04162010_27440.1)	
	10	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_06232011_27431.1)	
	11	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_07222010_27439.1)	
	12	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08252010_27438.1)	
	13	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_08262010_27437.1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	3	of	4	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	14	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09082010_27436.1)	
	15	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_09192011_27430.1)	
	16	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10042010_27435.1)	
	17	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10232012_27426.1)	
	18	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_10272013_27422.1)	
	19	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11012010_27434.1)	
	20	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11132009_27444.1)	
	21	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 10 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_11292011_27429.1)	
	22	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12182012_27425.1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	4	of	4	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	23	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_12212010_27443.1)	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/24/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Inventor Information for 16/055847

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE D.	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Grz

Search Another: Application # Search **or Patent #** Search **or International Registration #** Search

PCT / / Search **or PG PUBS #** Search

Attorney Docket # Search

Bar Code # Search

To Go BACK Use BACK Button on Your BROWSER Tool Bar
Back to PALM | ASSIGNMENT | OASIS | Home page

EAST Search History

/J.L./

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2494	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	USPAT	OR	ON	2020/03/24 23:27
L2	120	l1 with ((chimer$ or fusion) with vegf)	USPAT	OR	ON	2020/03/24 23:28
L3	15	(l1 l2) same (macular adj edema)	USPAT	OR	ON	2020/03/24 23:28
L4	70	aflibercept same (macular adj edema)	USPAT	OR	ON	2020/03/24 23:29
L5	155	yancopoulos-g$.in.	USPAT	OR	ON	2020/03/24 23:29
L6	1	aflibercept same (macular adj edema).clm.	USPAT	OR	ON	2020/03/24 23:29
L7	3	l5 and (macular adj edema).clm.	USPAT	OR	ON	2020/03/24 23:30

3/24/2020 11:31:21 PM
C:\Users\jlockard\Documents\EAST\Workspaces\16055847.wsp

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON3

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7070959	2006-07-04	Papadopoulos	
	2	8092803	2012-01-10	Furfine et al.	
	3	10406226	2019-09-10	Dix et al.	
	4	10464992	2019-11-05	Furfine et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2019/0388539	2019-12-26	Dix et al.	
	2	2020/0017572	2020-01-16	Furfine et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Anti-VEGF 2019: The State of the Art" Review of Ophthalmology (published August 5, 2019)	
	2	CHATZIRALLI et al. "Intravitreal aflibercept for neovascular age-related macular degeneration in patients aged 90 years or older: 2-year visual acuity outcomes" Eye (2018) 32:1523-1529	
	3	CHUNG et al. "Ziv-aflibercept: A novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer" Am J Heath-Syst Pharm (November 1, 2013) 70:1887-1896	
	4	COOPER et al., "Increased Renal Expression of Vascular Endothelial Growth Factor (VEGF) and Its Receptor VEGFR-2 in Experimental Diabetes" Diabetes (1999) 48:2229-2239	
	5	CROLL et al., "VEGF-mediated inflammation precedes angiogenesis in adult brain" Experimental Neurology (2004) 187:388-402	
	6	DeVRIESE et al., "Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes" J. Am. Soc. Nephrol (2001) 12:993-1000	
	7	EREMINA et al., "Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases" Journal of Clinical Investigation (March 2003) 111(5):707-716	
	8	ERIKSSON et al., "Structure, Expression and Receptor-Binding Properties of Novel Vascular Endothelial Growth Factors" Vascular Growth Factors and Angiogenesis, Springer (1999) pp. 41-57	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/055,847
				Filing Date	August 6, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON3

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	FERRARA, N. "Vascular Endothelial Growth Factor: Molecular and Biological Aspects" Advances in Organ Biology (1999) pp. 1-30	
	10	FERRARA et al., "Clinical applications of angiogenic growth factors and their inhibitors" Nature Medicine (December 1999) 5(12):1359-1364	
	11	FLYVBJERG et al., "Amelioration of Long-Term Renal Changes in Obese Type 2 Diabetic Mice by a Neutralizing Vascular Endothelial Growth Factor Antibody" Diabetes (October 2002) 51:3090-3094	
	12	HOLASH et al., "Vessel Cooption, Regression, and Growth in Tumors Mediated by Angiopoietins and VEGF" Science (June 18, 1999) 284(5422):1994-1998	
	13	KOROBELNIK et al., "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion" American Academy of Ophthalmology (2014) 121(1):202-208	
	14	MITCHELL, Edith P. "Targeted Therapy for Metastatic Colorectal Cancer: Role of Aflibercept" Clinical Colorectal Cancer (2013) 12(2):73-85	
	15	NOGUERA-TROISE et al., "Blockade of D114 inhibits tumour growth by promoting non-productive angiogenesis" Nature (December 2006) 444:1032-1037	
	16	RUDGE et al., "VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade" PNAS (November 20, 2007) 104(47):18363-18370	
	17	SCHMIDT-ERFURTH et al., "Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration" Ophthalmology (2014) 121:193-201	
	18	SEMERARO et al., "Aflibercept in wet AMD: specific role and optimal use" Drug Design, Development and Therapy (August 2, 2013) 7:711-722	
	19	TANNOCK et al., "Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomized trial" Lancet Oncol (2013) 14:760-768	
	20	THURSTON, Gavin "Complementary actions of VEGF and Angiopoietin-1 on blood vessel growth and leakage" J. Anat. (2002) 200:575-580	
	21	XIA et al., "Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis" Blood (July 1, 2003) 102(1):161-168	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Eye (2018) 32:1523–1529
https://doi.org/10.1038/s41433-018-0114-3

The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE

Intravitreal aflibercept for neovascular age-related macular degeneration in patients aged 90 years or older: 2-year visual acuity outcomes

Irini Chatziralli[1] · Shane O. Regan[2] · Ryian Mohamed[3] · James Talks[4] · Sobha Sivaprasad[1] UK Aflibercept Users Group

Received: 21 October 2017 / Revised: 18 February 2018 / Accepted: 8 April 2018 / Published online: 4 June 2018

Abstract

Purpose The purpose of this study was to investigate the efficacy of intravitreal aflibercept for neovascular age-related macular degeneration (nAMD) in very elderly patients aged 90 years or older at 2 years after treatment initiation.

Methods In this multicentre retrospective data analysis from electronic medical record, consecutive treatment-naive patients with nAMD treated with aflibercept with at least 2 years follow-up were stratified into those aged < 90 years (Group I) and an older cohort aged 90 and over (Group II). We compared the visual acuity (EDTRS letters) outcomes at 4 weekly intervals between the two groups over a 2-year period.

Results The mean visual acuity of Group I at presentation was 56.3 ETDRS letters versus 52.8 letters in Group II. Maximal visual acuity was achieved in both the groups by 6 months after initiating treatment (4.7 vs. 4.0 letters gain). By 2 years, the mean visual acuity of the older cohort fell marginally below their baseline visual acuity (0.8 letter loss), while Group I presented +2.1 letters gain. The number of injections given and the retention rate of the older cohort were no different to the rest of the patients.

Conclusions Very old patients with nAMD benefited from aflibercept, but not to the same degree as the younger patients. The study showed that, on an average, the very elderly patients were able to adhere to the intensive anti-VEGF treatment regimens.

Introduction

Age-related macular degeneration (AMD) is broadly classified into early and late forms. Late AMD is the leading cause of visual loss in the elderly. AMD is a perfect example of an aging-dependent condition, where the prevalence of the disease increases monotonically with age [1]. The prevalence of late AMD increases from 1% at 70 years to as high as 12% in patients over 80 years [2–4]. This condition is an outcome of a multitude of accumulating degenerative changes in the various layers of the outer retina and the choroid. Although there have been many well-conducted epidemiological studies on AMD, the proportions of patients aged 90 years or older in these cohorts were small. Therefore, there is a paucity of information on AMD in the very elderly patients.

Late AMD is further classified into "dry" and "wet or neovascular" (nAMD). The former is responsible for the majority of cases, but there are no treatment options available for this condition as yet. Only 10–15% of patients exhibit nAMD and these patients present with sudden decrease in vision, and if left untreated, this condition results in profound irreversible visual impairment [5, 6]. AMD is a bilateral disease and the risk of developing nAMD in the fellow eye of patients with unilateral AMD

Members of the UK Aflibercept Users Group are listed above References

✉ Sobha Sivaprasad
senswathi@aol.com

[1] National Institute for Health Research, Biomedical Research Centre at Moorfields Eye Hospital National Health Service Foundation Trust, London, UK

[2] University Hospital Limerick, Limerick, Ireland

[3] University College London Hospitals NHS Trust, London, UK

[4] Newcastle Upon Tyne Hospitals Foundation NHS Trust, Newcastle-upon-Tyne, UK

increases by 10% per year from the date of diagnosis, albeit this is dependent on features of the eye and other risk factors [7]. Furthermore, if a patient develops nAMD in one eye at the age of 80, the risk of nAMD in the fellow eye is 48% at 10 years [6]. Therefore, we would expect most patients with nAMD at 90 years to have bilateral nAMD. Determining the outcome of treatment in this cohort, compared to those in the younger age group, has implications, as it estimates the burden of this disease in this age group that is also at risk of other aging-dependent co-morbidities. Studying the treatment outcomes in this group will also provide us with better estimates of age-dependent outcomes of treatments for health economic evaluation. Ultimately, this has significant implications for future service provision, and treatment planning in the very elderly.

Intravitreal injections of inhibitors of vascular endothelial growth factor (VEGF) have been the mainstay of treatment for nAMD for over a decade [8–12] The three anti-VEGF agents commonly used for this condition include ranibizumab, bevacizumab and aflibercept. The treatment regimens are intensive with monthly intravitreal injections for 3 months, followed by varying re-treatment regimens depending on the anti-VEGF agent. On an average, a patient requires 7–8 injections in the first year and six injections from the second year. A comprehensive assessment of baseline predictive factors for visual outcomes at month 12 in Comparison of Age-related macular degeneration Treatment Trials (CATT) demonstrated that older age was associated with poor outcomes in both ranibizumab and bevacizumab groups, while the exact cause for this observation remains unknown [10]. Aflibercept is the newest FDA-approved anti-VEGF agent against nAMD, which binds tightly to VEGF-A, having a longer half-life than both ranibizumab and bevacizumab, a property which can be exploited by ophthalmologists to allow greater intervals between intravitreal treatments [12] The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW 1 and VIEW 2) showed that intravitreal aflibercept given bimonthly after 3 initial monthly doses had comparable improvement in visual acuity as monthly ranibizumab in treatment-naive patients with nAMD [12]

To our knowledge, the specific effect of older age on the efficacy of aflibercept in nAMD has not been addressed in the scientific literature, while older age has been shown to adversely affect the outcomes in patients treated with both bevacizumab and ranibizumab [10, 11] In addition, since it is difficult to study the outcomes in an elderly population due to several issues, including follow-up retention, large study samples are needed in order to reach reliable conclusions. Consequently, analysis of a large database system seems to be a good option. In fact, the use of electronic databases to estimate the outcomes in retinal disorders is becoming increasingly common, and they have been used to provide estimates for national and regional population outcomes [13, 14]. We have recently utilized a national dataset from 16 centres in the United Kingdom (UK) to report that the "real world" clinical outcomes of aflibercept in nAMD are similar to that of the randomized control trials of aflibercept in AMD [13] Therefore, this dataset is ideal to examine the influence of advanced age on visual outcomes in patients with nAMD treated with aflibercept. In this study, we compared aflibercept the outcomes in very elderly patients with nAMD (≥90 years) with the rest of the cohort treated with aflibercept for nAMD to evaluate the treatment's outcomes in the very old population.

Materials and methods

In this retrospective study, anonymised data was extracted from 16 UK National Health Service (NHS) hospitals forall treatment-naive eyes with nAMD initiated on aflibercept between March 2013 and April 2015, to ensure a minimum of 24-month follow-up. All the data were recorded using a single electronic medical record (EMR) system (Medisoft Ophthalmology; Medisoft Limited, Leeds, UK), which mandated the collection of a standardized dataset throughout the nAMD care pathway. Written approval for anonymised data extraction was received from each participating hospital. Ethical approval was not required, since a study of this nature is considered as an audit or service evaluation. The study was conducted in accordance with the tenets of Helsinki Declaration and the UK's Data Protection Act.

Sites were selected based on the confirmation that they used aflibercept to treat nAMD according to the VIEW protocol, consisting of 3-monthly intravitreal aflibercept injections (loading phase), followed by repeated bimonthly injections thereafter during theentire year 1 . All included centers were using a treat and extend approach after year 1. To determine the influence of age on visual acuity (VA) outcomes, patients were divided into two groups: Group I consisted of a younger cohort aged 0–89 years, while Group II consisted of very elderly patients aged 90 years and over.

All patients underwent optical coherence tomography (OCT) and fluorescein angiography to confirm the diagnosis of nAMD, while indocyanine green angiography was used at the discretion of the physician when needed. Eyes with polypoidal choroidal vasculopathy, choroidal neovascularization of other cause than nAMD, other co-morbidities that may confound visual outcomes and those treated previously with anti-VEGF were excluded. At each visit, visual acuity, injection history and follow-up date were recorded and entered into the EMR system by all staff members as part of routine clinical care. Potential operative and postoperative ocular and systemic complications were also documented at each visit.

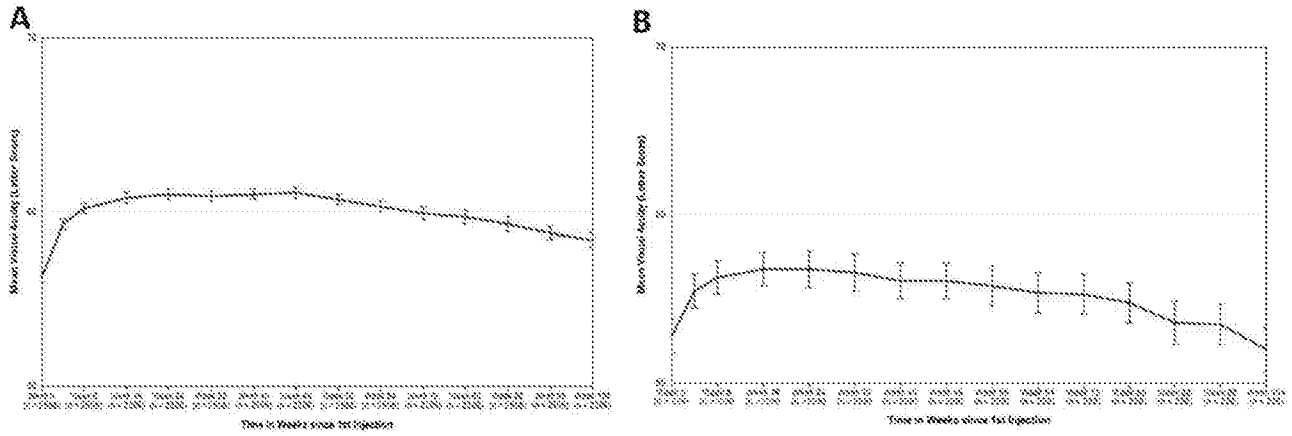


Fig. 1 Mean change in visual acuity over time in patients aged <90 years (**a**) and ≥90 years (**b**)

Visual acuity and missing value imputation

Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity letter scores at 2 meters were recorded at each visit at all sites, and represented the primary outcome of the study. In cases when alternatives measures were used conversion to ETDRS letters was performed. The visual acuity at each clinical visit was used for the analysis. When visual acuity recorded was counting figures, hand movements, light perception or no light perception, zero ETDRS letter score was ascribed.

Since in real-world studies, patients tend not to attend at the precisely intended intervals, the visual acuity of all attendees at 4-week intervals were utilized for the analysis over a 2-year period, having ensured that the sample size in each month reflected all patients who were being followed up continually. If there were gaps in the visual acuity data, they were imputed using the mean of the observations before and after the missing period. No observations were carried forward beyond the last recorded VA value, because loss to follow-up is more common in clinical practice than in proper clinical trials.

Results

Data were extracted from 16 NHS centers for 2734 treatment-naive eyes initiating aflibercept treatment for nAMD between March 2013 and April 2015, to allow a minimum follow-up of 2 years. Group I (aged < 90 years) comprised 2506 eyes and Group II (aged ≥ 90 years) included 228 (8.3%) eyes.

Mean change in visual acuity at 2 years

The mean change in VA over time for both the groups is shown in Fig. 1. In patients aged < 90 years, the mean VA at baseline was 56.3 ETDRS letters (standard error, 0.3 letter), improving significantly to 60.9 ETDRS letter at year 1 (standard error, 0.3 letter; + 4.6 letters gain) and to 58.4 ETDRS letter at year 2 (standard error, 0.4 letter; + 2.1 letters gain), compared to baseline. In patients aged ≥ 90 years, the VA at baseline was 52.8 ETDRS letters (standard error, 1 letter) and improved to 55.9 ETDRS letters at year 1 (standard error, 1.2 letter; + 3.1 letters gain), but dropped to 52 ETDRS letters at year 2 (standard error, 1.3 letter; −0.8 letters loss), compared to baseline. The maximum change in VA was achieved at 6 months for both the groups (+4.7 and +4.0 letters gain respectively).

First eye involvement

If analysis was restricted to first-treated eyes (eyes with normal vision in the other eye), in Group I the mean baseline VA for first-treated eyes was 55.2 ETDRS letters (standard error, 0.4 letter), which increased to 60.6 letters at year 1 (standard error, 0.4 letter; +5.4 letters gain) and to 58.1 letters (standard error, 0.5 letter; +5 letters gain) at year 2. In Group II, the mean baseline VA in first-treated eyes was 50.0 ETDRS letters (standard error, 1.2 letter), increasing to 52.4 letters at year 1 (standard error, 1.5 letter; +2.4 letters gain), but dropping to 48.8 letters at year 2 (standard error, 1.7 letter; −1.2 letters loss).

Second eye involvement

For second-treated eye (eyes with visual loss in other eye) in Group I, the mean baseline VA was 63.5 ETDRS letters (standard error, 0.7 letter), increasing to 65.1 letters at year 1 (standard error, 0.8 letter; +1.6 letters gain) and to 63.4 letters at year 2 (standard error, 0.8 letter; −0.1 letter loss). In Group II, the mean baseline VA for second-treated eye was 59.2 ETDRS letters (standard error, 2.4 letter), which increased to 63.0 letters at year 1 (standard error, 2.2 letter;

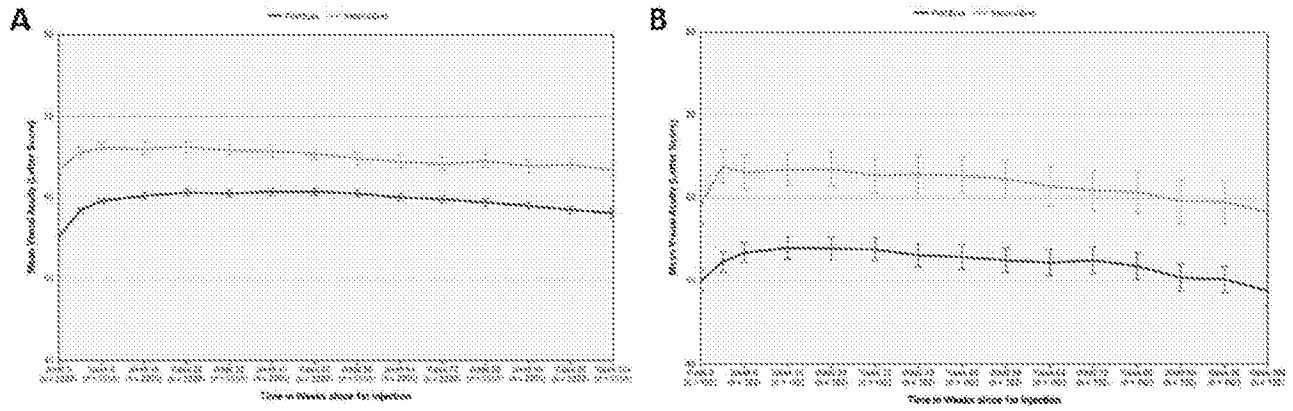


Fig. 2 Mean change in visual acuity over time regarding first-treated and second-treated eyes in patients aged <90 years (**a**) and ≥90 years (**b**)

+3.8 letters gain) and dropped to 58.3 letters at year 2 (standard error, 2.5 letter; −0.9 letter loss), as it is shown in Fig. 2.

Patients presenting poor visual acuity

There were 218 eyes (13.0%) in Group I, compared to 24 eyes (10.5%) in Group 2 that presented with VA < 35 ETDRS letters. For both the groups, the largest VA gains were achieved in eyes that started with the worst vision. In patients aged < 90 years, eyes with baseline VA < 35 ETDRS letters gained a mean of 11.6 letters (standard error, 1.1 letter) and 9.2 letters (standard error, 1.2 letter) at year 1 and 2 respectively. A similar trend was observed in patients aged ≥ 90 years with eyes commencing aflibercept treatment, with the worst VA attaining the largest VA gains, but to a lesser degree. Specifically, patients in Group II with baseline VA < 35 ETDRS letters gained a mean of 7.4 letters (standard error, 1.9 letter) and 3.9 letters (standard error, 3.4 letter) at year 1 and 2, respectively.

Patients presenting good vision

There were 397 patients (15.8%) in Group I, compared to 24 (10.5%) patients in Group II who presented VA > 70 ETDRS letters. In Group I, there was a mean decline of 0.6 letters (standard error, 0.4 letter) and 3.5 letters (standard error, 0.6 letter) at year 1 and 2, respectively, as it is depicted in Fig. 3a. In Group II, patients with baseline VA > 70 ETDRS letters (24 eyes) experienced a significant drop in VA of 3.8 letters at 1 year (standard error, 1.7 letter) and 13.3 letters at year 2 (standard error, 3.4 letter), as shown in Fig. 3b.

Gains in visual acuity

In Group I, the proportions of the 2147 eyes (85.7%) with follow-up at year 1 that gained 5, 10 and 15 letters were 52.3%, 35.2% and 20.6%, respectively. At year 2, the proportions of the 2102 eyes (83.9%) with a gain of 5, 10 and 15 letters were 46.7%, 31.5% and 20.7%, respectively. In patients aged ≥ 90 years, the proportions of 186 eyes (81.6%) with follow-up at 1 year that gained 5, 10 and 15 letters were 49.5%, 32.8% and 22.6%, respectively. At year 2, the proportions of the 192 eyes (84.2%) gaining 5, 10 and 15 letters were 37.5%, 27.6% and 17.7%, respectively (Fig. 4).

Losers in visual acuity

Over the first year, the proportions of those losing 5, 10 and 15 letters in Group I were 18.8%, 10% and 5.8%, respectively and at 2 years, 26.3%, 18.3% and 13% lost 5, 10 and 15 letters. In Group II, the proportions losing 5, 10 and 15 letters were 26%, 14% and 7%, respectively at year 1 and 37%, 24% and 16% of eyes in year 2, respectively.

Discussion

This study evaluated aflibercept outcomes in nAMD in the largest series of patients aged 90 years or over. The principal message of this study is that intravitreal aflibercept is effective in the very elderly population with nAMD and they are able to adhere to rigorous anti-VEGF treatment regimens.

There are half a million people aged 90 years or older in the UK. Owen et al reported ~40,000 new nAMD cases a year in the UK, with an estimated 7700 people beingin this age group (19%) [4]. This study shows that the oldest people constituted 8% of the new cases presented, and were treated with aflibercept over 2 years. Therefore, approximately half the expected number of the very elderly patients with new onset nAMD were present for the treatment. Considering those who presented for diagnosis and

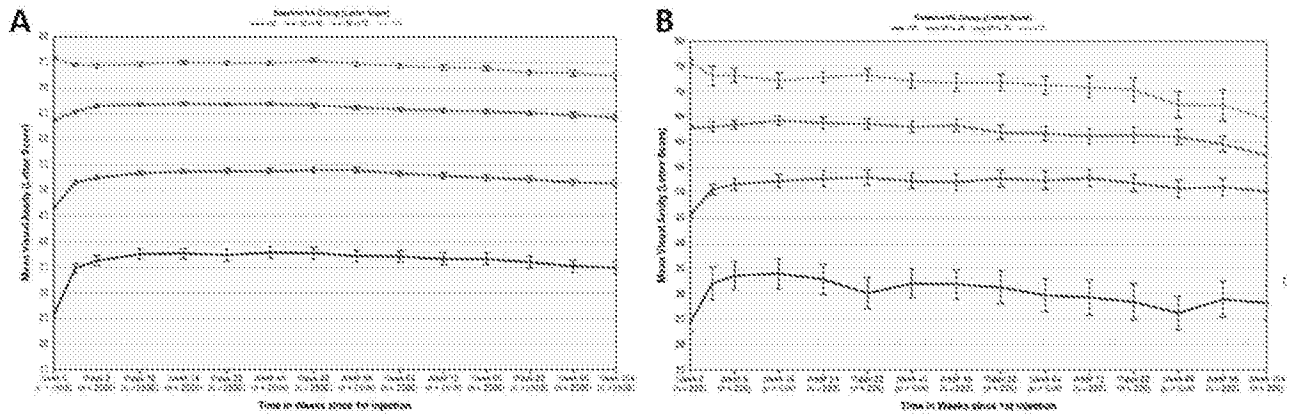


Fig. 3 Mean change in visual acuity over time based on baseline visual acuity groups in patients aged <90 years (**a**) and ≥90 years (**b**)

treatment, their baseline VA was similar to the rest of the cohort. Therefore, those were the patients who were able to access the NHS benefit from the treatment received for nAMD.

The proportion of patients with final VA records at 2 years was also similar between the two the groups, suggesting that the drop out rate was not higher in the very old patients. The study is limited to 2-year follow-up. Longer follow-up of these patients will provide insight into any deviations between the two cohorts on clinic attendance with time. The outcome measured in various ways show that very elderly patients with nAMD benefit from aflibercept therapy. However, it is more challenging for the patients aged 90 years or above to achieve the driving vision, defined as more than 70 letters in the treated eyes. In addition, the older patients who presented good vision (>70 letters) showed a larger decline in VA over the 2 years, compared to the rest of the cohort. These outcomes in this age group may contribute to the higher risk of falls and fractures, need for nursing home support and mortality.

Interestingly, we also observed that 80% of patients presented first eye involvement in the 90 years and above group. We postulate that this group may indeed represent a unique "special" group that has avoided conversion to nAMD, probably having a lower predisposition for the development of nAMD. It would be useful to interrogate this group of patients further in terms of both functional and structural changes in the retina to study the disease mechanism.

The VA outcomes of the present study were not as favorable as the clinical trials outcomes, but were similar to the other real-life studies [13, 15, 16] The mean gain in VA in our study in patients aged < 90 years was +4.6 and +2.1 letters at year 1 and 2, respectively. In patients aged ≥ 90 years, the mean gain in VA at year 1 was +3.1 letters, while patients lost 0.8 letters at year 2. The integrated analysis of VIEW 1 and VIEW 2 studies showed 8.4 letters gain at year 1 (7.9 letters for VIEW 1 and 8.9 letters for VIEW 2 study [12], whereas Talks et al found 5.1 letters gain at year 1 in patients with nAMD treated with intravitreal aflibercept in real-life conditions, based on the VIEW protocol [13]. Additionally, previous audits using PRN ranibizumab in clinical practice reported VA gains of 2–3.8 letters at year 1 [15, 16]. It is worthy to note that reduced VA in the older group may represent more prevalent concurrent atrophic changes than in the younger group. In addition, the aged outer retinal tissue may be less responsive to anti-VEGF therapy.

The discrepancy in the VA outcomes between clinical trials and real-life studies may be explained by the fact that in the real-world, data measurement techniques may differ. Specifically, VA is usually measured with the patients' habitual correction and not with the subjective refraction at each visit as in clinical trials. Although this may underestimate the actual changes in vision, it may reflect better patients' vision experience [13]. Moreover, patients in clinical trials are strictly selected and may have different characteristics than those of daily practice, while treatment is administered within tight timelines. It is also worthy to note that this older patient cohort is often not included in the clinical trials, even though these diseases are aging dependent. They represented 8% of this cohort. Therefore, this is an example where the answers to a research question are better derived from real-life datasets than clinical trials.

Another interesting observation of our study was that maximal VA gain was obtained at month 6 after initiation of treatment, irrespective of the age. In addition, the initial VA gain achieved after the 3-monthly loading phase was maintained at the end of year 1 in both the groups and by year 2 in patients aged < 90 years. In contrast, in the very elderly patients, the rate of decline in VA was more pronounced after year 1, with patients presenting loss of 0.8 letters at year 2 and falling below the baseline VA. However, the outcome is still better than the natural history of the disease. Although treatment after 6 months did not result in further VA gains in either group, continuous treatment may halt further visual deteriorations in both the groups.

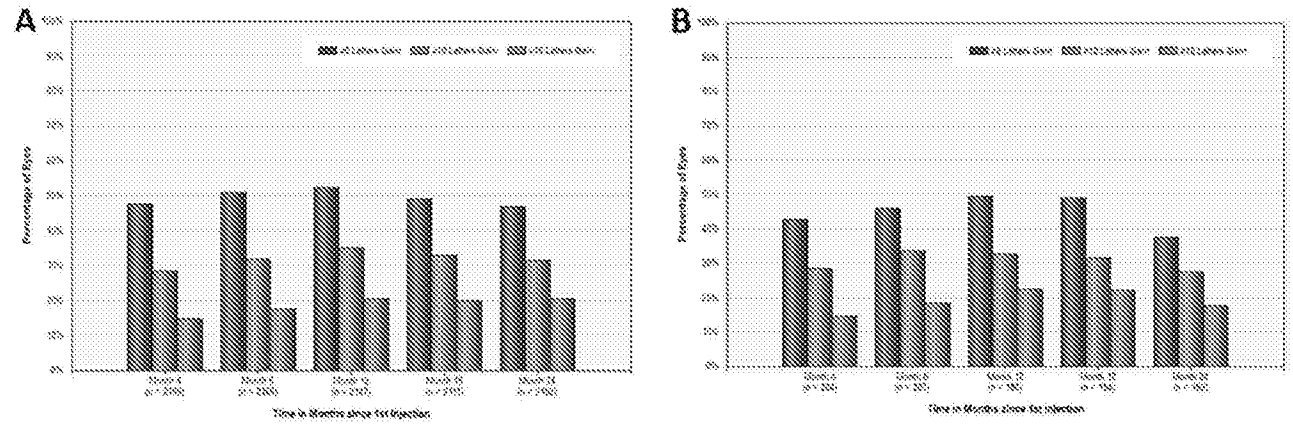


Fig. 4 Percentage of patients gaining at least 5, 10 and 15 letters in patients aged <90 years (**a**) and ≥90 years (**b**)

In conclusion, our study showed that very old patients with nAMD benefited from aflibercept therapy, but not to the same degree as the younger patients. The reason why elderly patients do not achieve the same outcomes as their younger counterparts despite adhering to the treatment regimen is unclear. An understanding of the morphological differences in patients with nAMD across different age profiles should shed more light on the disease mechanisms. The information provided in this study may also be of value to health economists for incorporation in future cost-effectiveness models.

Summary

What was known before

- Intravitreal aflibercept is safe and effective for the treatment of age-related macular degeneration.
- The so-far studies regarding the effectiveness of aflibercept in patients over 90 years are scarce.

What this study adds

- Very old patients with nAMD benefited from aflibercept, but not to the same degree as younger the patients.
- The study showed that on an average, the very elderly patients are able to adhere to the intensive anti-VEGF treatment regimens.

UK Aflibercept Users Group A. J. Lotery, F. Ghanchi, N. Patel, C. Bailey, S. Mahmood, A. Lobo, B. Paul, Q. Kashif, C. Santiago, G. Walters, M. Tahir, B. Mushtaq, K. Ahmed, M. McKibbin, S. Sivaprasad, and J. Talks

Compliance with ethical standards

Conflict of interest Irini Chatziralli, James Talks and Sobha Sivaprasad have received travel grants, research grants and speaker fees, and attended advisory board meetings of Bayer, Allergan and Novartis. The remaining authors declare that they have no conflict of interest.

References

1. Myall DJ, Pitcher TL, Pearson JF, Dalrymple-Alford JC, Anderson TJ, MacAskill MR. Parkinson's in the oldest old: Impact on estimates of future disease burden. Park Relat Disord. 2017. https://doi.org/10.1016/j.parkreldis.2017.06.018.
2. Colijn JM, Buitendijk GHS, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, et al. Prevalence of age-related macular degeneration in europe: the past and the future. Ophthalmology . 2017. https://doi.org/10.1016/j.ophtha.2017.05.035
3. Bunce C, Xing W, Wormald R. Causes of blind and partial sight certifications in England and Wales: April 2007-March 2008. Eye . 2010;24:1692–9.
4. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. Br J Ophthalmol. 2012;96:752–6.
5. Ferris FL 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology . 2013;120:844–51.
6. Chew EY, Clemons TE, Agrón E, Sperduto RD, Sangiovanni JP, Davis MD, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. JAMA Ophthalmol. 2014;132:272–7.
7. Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL 3rd. ; Age-Related Eye Disease Study Research Group. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report. Ophthalmology. 2005;112:533–9.
8. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419–31.
9. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1432–44.
10. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897–908.
11. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet . 2013;382:1258–67.

12. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119: 2537–48.
13. Talks JS, Lotery AJ, Ghanchi F, Sivaprasad S, Johnston RL, Patel N, et al. First-year visual acuity outcomes of providing aflibercept according to the VIEW Study Protocol for age-related macular degeneration. Ophthalmology . 2016;123:337–43.
14. Barthelmes D, Nguyen V, Daien V, Campain A, Walton R, Guymer R, et al. Two year outcomes of "treat and extend" intravitreal therapy using aflibercept preferentially for neovascular age-related macular degeneration. Retina . 2017. https://doi.org/10.1097/IAE.0000000000001496.
15. Pushpoth S, Sykakis E, Merchant K, Browning AC, Gupta R, Talks SJ. Measuring the benefit of 4 years of intravitreal ranibizumab treatment for neovascular age-related macular degeneration. Br J Ophthalmol. 2012;96:1469–73.
16. Holz FG, Tadayoni R, Beatty S, Berger A, Cereda MG, Cortez R, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol. 2015;99:220–6.

Ziv-aflibercept: A novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer

CLEMENT CHUNG AND NISHA PHERWANI

Purpose. The pharmacology, pharmacokinetics, clinical efficacy, safety, and administration of ziv-aflibercept in combination therapy for metastatic colorectal cancer (mCRC) are reviewed.

Summary. Ziv-aflibercept (Zaltrap, Regeneron Pharmaceuticals and sanofi-aventis) is a novel recombinant fusion protein that targets the angiogenesis signaling pathway of tumor cells by blocking vascular endothelial growth factor (VEGF) receptors that play a key role in tumor growth and metastasis; it is a more potent VEGF blocker than bevacizumab. Ziv-aflibercept is approved by the Food and Drug Administration for use in combination with fluorouracil, irinotecan, and leucovorin (the FOLFIRI regimen) for second-line treatment of patients with mCRC who have disease progression during first-line oxaliplatin-based chemotherapy. A Phase III trial demonstrated that relative to FOLFIRI therapy alone, the use of ziv-aflibercept was associated with significantly improved patient response, overall survival, and progression-free survival in patients with good performance status at baseline, including some who had received prior bevacizumab therapy. The most common grade 3 or 4 adverse effects associated with ziv-aflibercept use in clinical studies were neutropenia, hypertension, and diarrhea; the U.S. product labeling warns of potential hemorrhage and other treatment-related risks.

Conclusion. Current clinical data are insufficient to directly compare ziv-aflibercept and bevacizumab when used with standard combination chemotherapy as first- or second-line regimens for mCRC. The role of ziv-aflibercept is currently limited to the second-line setting in combination with irinotecan-based regimens in mCRC patients who have not received irinotecan previously. The role of ziv-aflibercept in chemotherapy for other tumor types is yet to be determined.

Am J Health-Syst Pharm. 2013; 70:1887-96

Cancers of the colon and rectum (collectively, colorectal cancer) comprise the third most common tumor type worldwide, with the former being more prevalent than the latter.[1] Colorectal cancer is the third most common form of cancer in the United States and the second most common cause of cancer-related deaths[2]; an estimated 143,460 new cases and 51,690 deaths occurred in 2012.[3] It is estimated that 20% of patients with colorectal cancer have metastatic disease at the time of diagnosis. Despite optimal treatment with adequate surgery and adjuvant chemotherapy, 30–50% of patients with primary colon cancer relapse and die from metastatic disease.[4,5] For most patients with metastatic colorectal cancer (mCRC), treatment remains palliative and the five-year survival rate is disappointing, at approximately 10%.[4]

First-line treatment of mCRC typically consists of fluorouracil and leucovorin (abbreviated FO, for folinic acid, in regimen acronyms) combined with either an oxaliplatin-based regimen (i.e., FOLFOX chemotherapy) or an irinotecan-based regimen (i.e., FOLFIRI), with crossover to the alternative regimen for second-line treatment (i.e., first-line FOLFOX followed by second-line FOLFIRI chemotherapy or vice versa).[6] Various trials have demonstrated no significant difference between FOLFOX and FOLFIRI chemotherapy in terms of the average response rate (54% and 56%, respectively), progression-free survival (PFS) (8.0 months versus 8.5 months), and overall survival (OS) (20.6 months versus 21.5 months) in patients with mCRC.[7-9] However,

CLEMENT CHUNG, PHARM.D., BCOP, BCPS, is Oncology Clinical Pharmacist, Lyndon B. Johnson General Hospital, Harris Health System, Houston, TX. NISHA PHERWANI, PHARM.D., BCOP, is Clinical Director, Oncology, Cardinal Health Pharmacy Solutions, Houston, TX 77077.

Address correspondence to Dr. Chung at the Lyndon B. Johnson General Hospital, 5656 Kelley Street, Houston, TX 77026 (clement_t_chung@yahoo.com).

The authors have declared no potential conflicts of interest.

 1079-2082/13/1101-1887$06.00.
DOI 10.2146/ajhp130143