

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: 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.

Brown #06-2655 – Supplementary Appendix

Methods and Supplementary Tables

METHODS

Study Design

Patients were enrolled at 83 investigative sites: 71 in the US, 8 in Europe (1 in the Czech Republic, 3 in France, 3 in Germany, 1 in Hungary), and 4 in Australia. In this 2-year study, the prespecified primary analysis was at 1 year. Predominantly classic lesions were defined as those where the classic component made up 50 percent or more of the total lesion area, which could include additional components such as contiguous subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and fibrosis in addition to choroidal neovascularization. An independent data monitoring committee met regularly one or more times a year during the study to review unmasked safety summaries prepared by an external statistical coordinating center. The study could be stopped for safety reasons but not for efficacy. After performing the primary analyses of the study (at 1 year) and with the recommendation of the data monitoring committee, the study protocol was amended on December 12, 2005, to offer patients in the PDT group the opportunity to crossover to receive ranibizumab (0.3 mg) without unmasking of study treatment.

Institutional Review Board, National Competent Authority, or Ethics Committee approval was obtained at each participating clinical center prior to the

start of the study. All US study sites were HIPAA compliant. Prior to determination of eligibility for enrollment (see Table 5 of the Supplementary Appendix for complete eligibility criteria), patients provided written, informed consent for study participation. Eligibility screening could last up to 28 days.

Only patients at least 50 years old were enrolled. Key eligibility criteria for the study eye included subfoveal choroidal neovascularization secondary to AMD that, based on fluorescein angiography and fundus photography, was confirmed by an independent central reading center to be predominantly classic in composition and suitable for treatment with PDT; a total lesion size of 5400 μm or less in greatest linear dimension; and best corrected visual acuity of 20/40 to 20/320 (Snellen equivalent), assessed using Early Treatment Diabetic Retinopathy Study [ETDRS] charts at a starting test distance of 2 meters; absence of permanent structural damage to the central fovea; and no history of treatment for subfoveal neovascular AMD (including any prior PDT) that by its nature or timing might compromise valid assessment of the effects of the study treatment. Juxtafoveal or extrafoveal laser photocoagulation in the study eye more than 1 month prior to day 0 was acceptable. Prior PDT in the nonstudy eye more than 7 days before study day 0 was also acceptable. There were no exclusion criteria regarding preexisting cardio-, cerebro-, or peripheral vascular conditions.

Study Treatment

In the ranibizumab groups, sham PDT was achieved by an intravenous infusion of saline rather than verteporfin, followed by laser irradiation of the macula identical to

that in the active PDT group. Light without verteporfin was not expected to have any effect. To maintain masking, patients who had received saline as well as those who had received verteporfin were instructed to follow exposure-to-light-precautions after PDT administration according to the verteporfin package insert.

Ranibizumab was injected into the study eye every 30 ± 7 days for a total of 12 injections in the first year beginning on day 0; sham injections were administered on the same dosing schedule. An empty, needle-less syringe was used for sham injections, with pressure applied to the anesthetized and prepared eye at the site of a typical intravitreal injection. Pre- and postinjection procedures (described previously)¹⁴ were identical for ranibizumab and sham injections.

Double masking of treatment assignment necessitated at least two investigators per study site: an unmasked “injecting” ophthalmologist to administer the study treatments and a masked “evaluating” ophthalmologist to perform study assessments. All other study site personnel (except those assisting with study treatment administration), patients, and central reading center personnel were masked to treatment assignment.

Study Assessments

Best corrected visual acuity (measured with ETDRS charts at a distance of 2 meters and using a standardized refraction and testing protocol) and lesion characteristics (based on fluorescein angiography and fundus photography) were assessed at the regularly scheduled study visits. The primary efficacy end point was the proportion of patients who at 12 months lost fewer than 15 letters (approximately 3 lines) from

baseline visual acuity in the study eye. Other prespecified visual acuity end points assessed at 12 months included the proportion of patients who gained 15 or more letters from baseline, proportion of patients with a Snellen equivalent of 20/200 or worse, and mean change from baseline (letters) over time. Severe visual acuity loss (loss of 30 letters [approximately 6 lines] or more from baseline) was an exploratory efficacy end point. Prespecified secondary end points involving characteristics of the choroidal neovascular lesion were mean changes from baseline to Month 12 in the size of the classic choroidal neovascularization component and the total area of leakage from choroidal neovascularization (including leakage as well as intense, progressive retinal pigment epithelium staining). Mean changes in the area of choroidal neovascularization and the area of the entire lesion were exploratory efficacy end points.

Safety assessments included intraocular pressure measurement (before and 60 ± 10 minutes after each study treatment) and indirect ophthalmoscopy and slit-lamp examination (before each study treatment). The incidence and severity of ocular and nonocular adverse events (see Table 6 of the Supplementary Appendix for criteria for serious ocular adverse events, and Tables 2 and 3 of the Supplementary Appendix for grading scales for intraocular inflammation), changes and abnormalities in clinical laboratory parameters and vital signs, and immunoreactivity to ranibizumab were also assessed.

Statistical Analysis

Efficacy analyses were performed on an intent-to-treat basis (including all randomized patients and according to the treatment group to which they were assigned) using a last-observation-carried-forward method to impute missing data (primary analysis) and using observed data (exploratory sensitivity analysis). Pairwise treatment comparisons were performed using statistical methods adjusting for baseline visual acuity score (< 45 letters versus \geq 45 letters) and, for lesion morphologic end points, the baseline value of the lesion characteristic. Binary end points were analyzed using the Cochran χ^2 test.¹⁶ Mean changes from baseline were analyzed using an analysis of variance model for visual acuity end points and an analysis of covariance model for morphologic end points. The Hochberg-Bonferroni multiple comparison procedure¹⁷ was used to adjust for the two pairwise treatment comparisons of the primary end point. Safety analyses included all treated patients.

Sample size was determined based on a 1:1:1 randomization ratio, the Pearson χ^2 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 three planned safety interim analyses before the primary efficacy analysis). Monte Carlo simulations were used to evaluate the power of the test. The planned sample size of 426 would have provided 96 percent power to detect a statistically significant difference between one or both ranibizumab groups and the verteporfin PDT control group in the percentage of patients losing fewer than 15 letters at 12 months, assuming a rate of 84 percent in each ranibizumab group and 67 percent in the verteporfin PDT control group.

Table 1. Patient Disposition in ANCHOR Trial

	Verteporfin PDT (no., %)	Ranibizumab 0.3 mg (no., %)	Ranibizumab 0.5 mg (no., %)	Total (no., %)
Enrolled	---	---	---	423 (100)
Randomly assigned to treatment	143 (100)	140 (100)	140 (100)	423 (100)
Received randomized treatment	143 (100)	137 (97.9)	140 (100)	420 (99.3)*
Intent-to-treat patients for efficacy analyses	143 (100)	140 (100)	140 (100)	423 (100)
Included in safety evaluation	143 (100)	137 (97.9)	140 (100)	420 (99.3)
Completed Month 12 [†]	127 (88.8)	128 (91.4)	131 (93.6)	386 (91.3)
Withdrawn from the study on or prior to Month 12	10 (7.0)	10 (7.1)	5 (3.6)	25 (5.9)
Death	1 (0.7)	3 (2.1)	2 (1.4)	6 (1.4)
Adverse event	4 (2.8)	2 (1.4)	1 (0.7)	7 (1.7)
Lost to follow-up	1 (0.7)	0	1 (0.7)	2 (0.5)
Patient's decision	3 (2.1)	2 (1.4)	1 (0.7)	6 (1.4)
Physician's decision	1 (0.7)	2 (1.4)	0	3 (0.7)
Patient noncompliance	0	1 (0.7)	0	1 (0.2)

Table 1. Patient Disposition in ANCHOR Trial (cont'd)

	Verteporfin PDT (no., %)	Ranibizumab 0.3 mg (no., %)	Ranibizumab 0.5 mg (no., %)	Total (no., %)
Discontinued treatment [‡] prior to Month 12	14 (9.8)	13 (9.3)	9 (6.4)	36 (8.5)
Death	1 (0.7)	3 (2.1)	2 (1.4)	6 (1.4)
Adverse event	6 (4.2)	3 (2.1)	4 (2.9)	13 (3.1)
Lost to follow-up	1 (0.7)	0	1 (0.7)	2 (0.5)
Patient's decision	4 (2.8)	4 (2.9)	2 (1.4)	10 (2.4)
Physician's decision	1 (0.7)	2 (1.4)	0	3 (0.7)
Patient noncompliance	0	1 (0.7)	0	1 (0.2)
Patient's condition mandated other therapeutic intervention	1 (0.7)	0	0	1 (0.2)

* Three patients did not receive the randomly assigned treatment, one because of the patient's decision and two based on the physician's decision.

[†]Defined as having the visual acuity assessment in study eye at Month 12. Patients who missed the Month 12 visit but stayed in the study for the second year were not included.

[‡]Some patients remained in the study after treatment discontinuation.

Table 2. Grading Scales for Flare/Cells*

Flare	
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slit lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein detectable in the anterior chamber. This protein is visible only with careful scrutiny by an experienced observer using slit lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Mild amount of protein detectable in the anterior chamber. The presence of protein in the anterior chamber is immediately apparent to an experienced observer using slit lamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2–3+	Moderate amount of protein detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+.
4+	A large (severe) amount of protein is detectable in the anterior chamber. Similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It needs to be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood–aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignments for flare (e.g., 1+ flare with fibrin).

Table 2. Grading Scales for Flare/Cells* (cont'd)

Cells	
0	No cells are seen in any optical section when a large slit lamp beam is swept across the anterior chamber.
Trace	Rare (1–3) cells are observed when the slit lamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	3–10 cells/optical section are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
2+	10–25 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
3+	25–50 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

*Modified from Hogan MH, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47:155.

Table 3. Grading Scale for Vitreous Cells*†

Cells in Retroilluminated Field	Description	Grade
0–1	Clear	0
2–20	Few opacities	Trace
21–50	Scattered opacities	1
51–100	Moderate opacities	2
101–250	Many opacities	3
>251	Dense opacities	4

*Using a Hruby lens.

†Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. 2nd rev. ed. New York: Mosby, 1996, p. 64.

Table 4. Nonocular Hemorrhagic Adverse Events

MedDRA* Preferred Term	Verteporfin	Ranibizumab	Ranibizumab
	PDT (n = 143)	0.3 mg (n = 137)	0.5 mg (n = 140)
Total [†] — no. (%)	3 (2.1)	7 (5.1)	9 (6.4)
Epistaxis	2 (1.4)	2 (1.5)	1 (0.7)
Ecchymosis	0	0	3 (2.1)
Hematoma	0	1 (0.7)	1 (0.7)
Subdural hematoma	0	2 (1.5)	0
Hematuria	1 (0.7)	1 (0.7)	0
Duodenal ulcer hemorrhage	0	0	1 (0.7)
Gastric hemorrhage	0	0	1 (0.7)
Gastrointestinal hemorrhage	0	0	1 (0.7)
Hemarthrosis	0	0	1 (0.7)
Hematochezia	0	0	1 (0.7)
Hemothorax	0	1 (0.7)	0
Lower gastrointestinal hemorrhage	0	1 (0.7)	0
Peritoneal hemorrhage	0	1 (0.7)	0

*Medical Dictionary for Regulatory Activities.

[†] The number of patients with any nonocular hemorrhagic adverse event.

Table 5. Eligibility Criteria for ANCHOR Study

Inclusion Criteria

- Age 50 years or older.
- Eligibility for treatment of study eye* with photodynamic therapy using verteporfin according to the VISUDYNE product labeling.
- Future treatment of study eye with photodynamic therapy using verteporfin anticipated or expected.
- Primary or recurrent subfoveal choroidal neovascular lesion secondary to age-related macular degeneration in the study eye
- A classic choroidal neovascularization component (well-demarcated hyperfluorescence boundaries in the early phase of the fluorescein angiogram) that is 50 percent or more of the total lesion size.
- Total lesion size 5400 μm or less in the greatest linear dimension.
- Best corrected visual acuity, using Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, of 20/40 to 20/320 (Snellen equivalent) in the study eye.

Exclusion Criteria

- Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy in the study eye.
 - Treatment with verteporfin in the nonstudy eye less than 7 days preceding day 0.
 - Previous participation in a clinical trial (for either eye) involving antiangiogenic drugs (pegaptanib, ranibizumab, anecortave acetate, protein kinase C inhibitors, etc.)
 - Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation) in the study eye.
 - Previous subfoveal focal laser photocoagulation in the study eye.
 - Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within 1 month preceding day 0.
 - History of vitrectomy surgery in the study eye.
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Table 5. Eligibility Criteria for ANCHOR Study (cont'd)

Exclusion Criteria (cont'd)

- History of submacular surgery or other surgical intervention for age-related macular degeneration in the study eye.
 - Previous participation in any studies of investigational drugs within 1 month preceding day 0 (excluding vitamins and minerals).
 - Subretinal hemorrhage in the study eye that involves the center of the fovea, if the size of the hemorrhage is either 50 percent or more of the total lesion area or 1 or more disc areas in size.
 - Subfoveal fibrosis or atrophy in the study eye.
 - Choroidal neovascularization in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.
 - Retinal pigment epithelial tear involving the macula in the study eye.
 - Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either (a) require medical or surgical intervention during the 24-month study period to prevent or treat visual loss that might result from that condition, or (b) if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 24-month study period.
 - Active intraocular inflammation (grade trace or above) in the study eye.
 - Current vitreous hemorrhage in the study eye.
 - History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye.
 - History of idiopathic or autoimmune-associated uveitis in either eye.
 - Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
 - Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding day 0.
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Table 5. Eligibility Criteria for ANCHOR Study (cont'd)

Exclusion Criteria (cont'd)

- Aphakia or absence of the posterior capsule in the study eye. Previous violation of the posterior capsule in the study eye was also excluded unless it occurred as a result of YAG posterior capsulotomy in association with prior, posterior chamber intraocular lens implantation.
- Spherical equivalent of the refractive error in the study eye demonstrating more than –8 diopters of myopia. For patients who had undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye could not exceed –8 diopters of myopia.
- Uncontrolled glaucoma in the study eye (defined as intraocular pressure of 30 mmHg or more despite treatment with antiglaucoma medication).
- History of glaucoma filtering surgery or corneal transplant in the study eye.
- Premenopausal women not using adequate contraception.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.
- Current treatment for active systemic infection.
- History of allergy to fluorescein, not amenable to treatment.
- Inability to obtain fundus photographs or fluorescein angiogram of sufficient quality to be analyzed and graded by the central reading center.
- Inability to comply with study or follow-up procedures.

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

Table 6. Criteria for Serious (Sight-Threatening) Ocular Adverse Events*

- Adverse event causes a decrease in visual acuity of ≥ 30 letters (compared with the last assessment of visual acuity prior to the most recent treatment) lasting > 1 hour.
- Adverse event causes a decrease in visual acuity to the level of Light Perception or worse lasting > 1 hour postinjection/sham procedure.
- Adverse event requires surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- Adverse event is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis).
- In the opinion of the investigator, adverse event may require medical intervention to prevent permanent loss of sight.

*An adverse event meeting any one of these five criteria was considered serious.