Supplementary Appendix

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

Supplement to: Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.

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Table 1. Eligibility Criteria for MARINA Study

Inclusion Criteria

- Age 50 years or older.
- Active primary or recurrent subfoveal lesions with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye. “Active” was defined as meeting *any* of the following criteria: (1) exhibiting a ≥10% increase in lesion size, as determined by comparing a fluorescein angiogram performed within 1 month preceding Day 0, inclusive, with a fluorescein angiogram performed within 6 months preceding Day 0, inclusive; or (2) resulting in a visual acuity loss of >1 Snellen line (or equivalent) and occurring at any time within the prior 6 months; or (3) subretinal hemorrhage associated with CNV within 1 month preceding Day 0.
- Lesions with occult CNV component are permissible. However, if classic CNV (well-demarcated hyperfluorescence boundaries in the early phase of the fluorescein angiogram) is present, the area of classic CNV must be less than 50% of the total lesion size.
- The total area of CNV (including both classic and occult components) encompassed within the lesion must be 50% or more of the total lesion area.
- The total lesion area must be 12 disc areas or less in size.
- 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 photodynamic therapy, external-beam radiation therapy, or transpupillary thermotherapy in the study eye.
- Treatment with verteporfin photodynamic therapy 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.)

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Table 1. Eligibility Criteria for MARINA Study (cont'd)

Exclusion Criteria (cont'd)

- 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.
- History of submacular surgery or other surgical intervention for AMD 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 fovea, if the size of the hemorrhage is either 50% or more of the total lesion area or 1 or more disc areas in size.
- Subfoveal fibrosis or atrophy in the study eye.
- CNV 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.

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Table 1. Eligibility Criteria for MARINA Study (cont'd)

Exclusion Criteria (cont'd)

- History of idiopathic or autoimmune-associated uveitis in either eye.
- Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
- Aphakia or absence of the posterior capsule in the study eye.
- Spherical equivalent of the refractive error in the study eye demonstrating more than –8 diopters of myopia.
- Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding day 0.
- Uncontrolled glaucoma in the study eye (defined as intraocular pressure of 30 mmHg or more despite treatment with antiglaucoma medications.
- History of glaucoma filtering surgery in the study eye.
- History of 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 with diphenhydramine.
- 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.

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Table 2. Patient Disposition in MARINA Trial

	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg	Total
Enrolled	–––	–––	–––	716 (100)
Randomly assigned to treatment	238 (100)	238 (100)	240 (100)	716 (100)
Received randomized treatment*	236 (99.2)	238 (100)	239 (99.6)	713 (99.6)
Intent-to-treat patients for efficacy analyses	238 (100)	238 (100)	240 (100)	716 (100)
Included in safety evaluation	236 (99.2)	238 (100)	239 (99.6)	713 (99.6)
Completed Month 12†	212 (89.1)	226 (95.0)	226 (94.2)	664 (92.7)
Crossed over from Sham to 0.5 mg ranibizumab	12 (5.0)	----	----	----
At Month 22	5 (2.1)	----	----	----
At Month 23	7 (2.9)	----	----	----
Completed Study	190 (79.8)	210 (88.2)	215 (89.6)	615 (85.9)
Discontinued from study	48 (20.2)	28 (11.8)	25 (10.4)	101 (14.1)
Death	5 (2.1)	5 (2.1)	6 (2.5)‡	16 (2.2)
Adverse event	8 (3.4)§	3 (1.3)	5 (2.1)	16 (2.2)
Lost to follow-up	2 (0.8)	3 (1.3)	3 (1.3)	8 (1.1)
Patient's decision	20 (8.4)	15 (6.3)	10 (4.2)	45 (6.3)
Physician's decision	1 (0.4)	0	1 (0.4)	2 (0.3)
Noncompliance	1 (0.4)	1 (0.4)	0	2 (0.3)
Patient's condition mandated other therapeutic intervention¶	11 (4.6)	1 (0.4)	0	12 (1.7)

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