A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration

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Objective: To evaluate the safety and efficacy of intravitreal ranibizumab in a large population of subjects with neovascular age-related macular degeneration (AMD).

Design: Twelve-month randomized (cohort 1) or open-label (cohort 2) multicenter clinical trial.

Participants: A total of 4300 subjects with angiographically determined subfoveal choroidal neovascularization (CNV) secondary to AMD.

Methods: Cohort 1 subjects were randomized 1:1 to receive 0.3 mg (n = 1169) or 0.5 mg (n = 1209) intravitreal ranibizumab for 3 monthly loading doses. Dose groups were stratified by AMD treatment history (treatment-naïve vs. previously treated). Cohort 1 subjects were retreated on the basis of optical coherence tomography (OCT) or visual acuity (VA) criteria. Cohort 2 subjects (n = 1922) received an initial intravitreal dose of 0.5 mg ranibizumab and were retreated at physician discretion. Safety was evaluated at all visits.

Main Outcome Measures: Safety outcomes included the incidence of ocular and nonocular adverse events (AEs) and serious adverse events (SAEs). Efficacy outcomes included changes in best-corrected VA over time.

Results: Some 81.7% of cohort 1 subjects and 49.9% of cohort 2 subjects completed the 12-month study. The average total number of ranibizumab injections was 4.9 for cohort 1 and 3.6 for cohort 2. The incidence of vascular and nonvascular deaths during the 12-month study was 0.9% and 0.7% in the cohort 1 0.3 mg group, 0.8% and 1.5% in the cohort 1 0.5 mg group, and 0.7% and 0.9% in cohort 2, respectively. The incidence of death due to unknown cause was 0.1% in both cohort 1 dose groups and cohort 2. The number of vascular deaths and deaths due to unknown cause did not differ across cohorts or dose groups. Stroke rates were 0.7%, 1.2%, and 0.6% in the 0.3 mg and 0.5 mg groups and cohort 2, respectively. At month 12, cohort 1 treatment-naïve subjects had gained an average of 0.5 (0.3 mg) and 2.3 (0.5 mg) VA letters and previously treated subjects had gained 1.7 (0.3 mg) and 2.3 (0.5 mg) VA letters.

Conclusions: Intravitreal ranibizumab was safe and well tolerated in a large population of subjects with neovascular AMD. Ranibizumab had a beneficial effect on VA. Future investigations will seek to establish optimal dosing regimens for persons with neovascular AMD.

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Neovascular age-related macular degeneration (AMD) is characterized by new vessel growth and leakage in the choroidal vascular network beneath the macula, with extension and leakage into the subretinal space. Although the pathologic events that precede choroidal neovascularization (CNV) are not clearly understood, disrupting the activity of vascular endothelial growth factor A (VEGF-A), a diffusible cytokine that promotes angiogenesis and vascular permeability, effectively treats CNV secondary to AMD.

Ranibizumab (LUCENTIS, Genentech, Inc., South San Francisco, CA) is a recombinant, humanized monoclonal antibody antigen-binding fragment (Fab) that neutralizes all active forms of VEGF-A. In 2 pivotal phase III trials—Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[1] and Anti-Vascular Endothelial Growth Factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in Age-related Macular Degeneration (ANCHOR)[2]—monthly intravitreal injections of 0.3 mg or 0.5 mg ranibizumab not only prevented vision loss but also improved visual acuity (VA) in patients with minimally classic or occult without classic and predominantly classic CNV, respectively. In those studies, ranibizumab treatment was associated with a low rate of serious adverse events (SAEs), including those attributable to systemic VEGF inhibition.

The Safety Assessment of Intravitreous Lucentis for AMD (SAILOR) study was a phase IIIb follow-up study to the MARINA and ANCHOR studies to evaluate the long-term safety and efficacy of ranibizumab in a large population of subjects with all subtypes (minimally classic, occult without classic, and predominantly classic) of neovascular AMD. SAILOR included more than 5 times as many ranibizumab-treated subjects as the MARINA and ANCHOR studies combined. Thus, it is the largest multicenter randomized study to date to evaluate safety and efficacy outcomes of anti-VEGF treatment in wet AMD, and it is the only phase III study to examine individualized, criteria-based retreatment.

Materials and Methods

SAILOR was a 12-month, multicenter, phase IIIb study intended to further characterize the safety and efficacy profiles of intravitreal ranibizumab. Protocols were approved by the institutional review board at each study site, and the study was conducted according to the International Conference on Harmonisation E6 Guideline for Good Clinical Practice and any national requirements. All subjects provided informed consent before participation in the study. The SAILOR study is registered at www.clinicaltrials.gov (NCT00251459; accessed February 5, 2009).

Two study cohorts were enrolled. Cohort 1 subjects were randomized 1:1 to receive 0.3 mg or 0.5 mg intravitreal ranibizumab. Cohort 2 subjects received open-label 0.5 mg intravitreal ranibizumab. Eligible subjects were ≥50 years of age with 20/40 to 20/400 (Snellen equivalent) best-corrected VA in the study eye. Cohort 1 VA was assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. In the interest of conserving time and resources, VA for cohort 2 (under a less rigorous treatment and assessment schedule) was assessed using Snellen charts. All subjects had angiographically determined subfoveal CNV (minimally classic, occult without classic, predominantly classic) secondary to AMD (as determined by the investigating physician), with evidence of recent disease progression defined by any of the following: loss of ≥5 ETDRS letters (or ≥1 Snellen line) within 6 months before study initiation (i.e., day 0); 10% increase in the CNV lesion area determined by comparing a fluorescein angiogram performed within 1 month before day 0 with an angiogram performed within 6 months before day 0; subretinal hemorrhage associated with CNV within 1 month before day 0; or classic CNV comprising >50% of the CNV lesion area.

Key exclusion criteria included verteporfin photodynamic therapy, pegaptanib sodium, or other AMD therapy within 30 days before day 0; previous submacular surgery or other surgical intervention for AMD in the study eye; participation in an investigational drug (except vitamins and minerals) study within 30 days before day 0; previous participation in a ranibizumab clinical trial; intravitreal administration of bevacizumab within 30 days before day 0; or current use of systemic anti-VEGF agents. Also excluded were subjects with fibrosis or atrophy involving the foveal center of the treated eye in the absence of a new lesion; CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia; a tear in the retinal pigment epithelium of the study eye involving the macula; or any current intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the investigating physician's opinion, would require medical or surgical intervention during the 12-month study period or, if allowed to progress untreated, would likely contribute to the loss of at least 2 Snellen equivalent lines of VA over the 12-month study period. Subjects with a history of cardiovascular disease were not excluded if their disease was controlled.

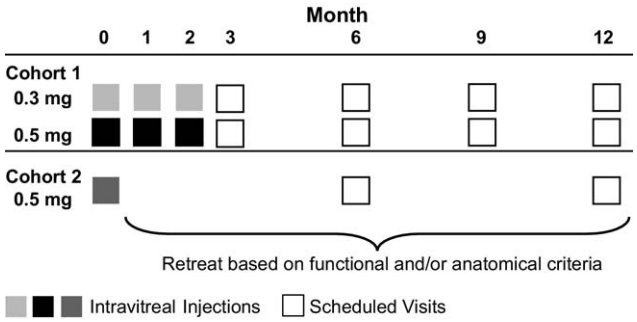

Figure 1. Study treatment and assessments. Cohort 1 subjects received 3 loading doses of ranibizumab and were retreated on the basis of VA (>5 letter decrease in VA from highest score at prior visits) or VA and/or OCT (>100 μm increase in CFT from the lowest measurement at prior visits) criteria. Cohort 2 subjects received 1 dose of ranibizumab on day 1 and were retreated at physician discretion. CFT = central foveal thickness; OCT = optical coherence tomography; VA = visual acuity.

Cohort 1 subjects were randomized 1:1 to receive 0.3 mg or 0.5 mg intravitreal ranibizumab. To prevent bias in reporting AEs, subjects were masked to treatment dose. (Because SAILOR was not designed with efficacy as an objective, physicians and study monitors were not masked.) Randomization was stratified according to treatment history. "Previously treated" subjects had previously received treatment AMD. "Treatment-naïve" subjects were newly diagnosed with neovascular AMD. Cohort 1 subjects received 3 monthly loading doses of intravitreal ranibizumab (day 0, month 1, and month 2) with scheduled follow-up visits at months 3, 6, 9, and 12 (Fig 1). If, at any time, the investigating physician believed that the between-visit interval was too long for a patient to go without being assessed, an unscheduled visit could occur. After the 3 loading doses, retreatment was based on (1) VA (a >5 ETDRS letter decrease in VA compared with the highest VA score at any prior scheduled visit) or (2) VA (same as above) and/or optical coherence tomography (OCT) (a >100-μm increase in central foveal thickness [CFT] compared with the lowest measurement at any previous scheduled study visit, with intraretinal or subretinal fluid present). Thus, OCT assessment was required only for retreatment option 2, in which case OCT data were consistently obtained at all study visits. Retreatment was to occur no more frequently than every 30 days. Before randomization, the investigating physician selected the retreatment criterion for each subject that was to be used throughout the study.

Cohort 1 subjects were evaluated with a full ocular examination and best-corrected VA (ETDRS chart at a distance of 4 m) and safety assessments on day 0 and at all scheduled (months 1, 2, 3, 6, 9, and 12) visits. Visual acuity assessments were required at unscheduled visits if a subject was being evaluated for retreatment. Safety assessments were required at all unscheduled visits.

Cohort 2 included both previously treated and treatment-naïve subjects. Subjects received 0.5 mg of ranibizumab, with an initial injection on day 0 and retreatment at the investigating physician's discretion, no more frequently than every 30 days. Cohort 2 subjects were evaluated for Snellen VA at day 0 and months 6 and 12. At unscheduled visits, VA was assessed at the investigating physician's discretion. Serious adverse events and adverse events (AEs) were assessed at scheduled and unscheduled visits, with formal safety assessments scheduled for months 6 and 12.

Adverse events included any unfavorable or unintended sign, symptom, or disease temporally associated with use of study drug or other protocol-imposed intervention. An AE was classified as an SAE if it caused or led to death, required or prolonged subject hospitalization, resulted in persistent or significant disability or incapacitation, or was considered to be a significant medical event by the investigating physician.

One eye per subject (i.e., the study eye) was treated. After thoroughly cleansing the lid, lashes, periorbital area, and conjunctiva with povidone iodine, local anesthesia and antimicrobials (ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution) were administered to the study eye. A 30-gauge, 0.5-inch needle attached to a low-volume syringe containing 50 μL of ranibizumab solution was inserted through the conjunctiva and sclera, 3.5 to 4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming toward the center of the globe. The injection volume was delivered slowly. The needle was slowly removed, ensuring that all drug solution was in the eye. Immediately after the injection, antimicrobial drops were administered, and the subject was instructed to self-administer antimicrobial drops 4 times daily for 3 days. The study eye was assessed with a finger count test and intraocular pressure within 15 and 70 minutes, respectively, of the ranibizumab injection.

The primary safety end point for cohort 1 was incidence of ocular and nonocular SAEs evaluated through month 12. A secondary safety end point was incidence of ocular and nonocular AEs evaluated through month 12. Efficacy end points for cohort 1 included change from baseline VA, proportion of subjects who gained ≥15 VA letters from baseline, and change from baseline CFT across the study period.

The primary safety end points for cohort 2 were the incidence of ocular and nonocular SAEs and AEs evaluated through month 12. Efficacy outcomes for cohort 2 included median change in Snellen VA from baseline and the proportion of subjects with Snellen 20/200 or worse at baseline compared with months 6 and 12.

Statistical Analysis

Safety and efficacy analyses included all subjects who received at least 1 injection of ranibizumab. Incidence of ocular and nonocular SAEs and AEs and 95% 2-sided confidence intervals for key SAEs were determined for both cohorts and each dose group. No formal hypothesis testing was conducted to compare cohorts, dose groups, or treatment-naïve and previously treated subjects. A sample of 2378 cohort 1 subjects and 1922 cohort 2 subjects was considered sufficient to estimate rates of uncommon SAEs and AEs.

Efficacy results for cohort 1 were stratified by dose group and treatment history. Estimated proportions were obtained for dichotomous end points. Continuous end points were evaluated using descriptive statistics, including mean, median, standard deviation, standard error, and range.

To further evaluate stroke rates across cohorts and dose groups, each subject's medical history was reviewed, and subjects were classified by preexisting conditions that may have been associated with the incidence of stroke during the 12-month study. These included prior stroke, myocardial infarction (MI), hypertension, transient ischemic attack, coronary artery disease, arrhythmias, valve malfunction, congestive heart failure, angioplasty, deep vein thrombosis, diabetes, endocardectomy, cardiac inflammation, prior stent, and use of aspirin, lipid-lowering drugs, anticoagulants, or platelet aggregation inhibitors. A univariate Cox proportional hazard regression model was used to identify which of those were significant (i.e., $P \leq 0.05$) risk factors for stroke in SAILOR. In addition, models that included the interaction of dose with each of the significant risk factors were fit separately.

Missing Data

Missing data were not imputed for safety end points. For cohort 1, missing values for efficacy end points were imputed using the last-observation-carried-forward method. For cohort 2, missing Snellen values were not imputed.

Results

From November 2005 to June 30, 2006 (when ranibizumab was approved for the treatment of neovascular AMD by the Food and Drug Administration), 2378 cohort 1 subjects were randomly assigned to receive 0.3 mg (n = 1169) or 0.5 mg (n = 1209) intravitreal ranibizumab at 105 US centers. Cohort 1 subjects had an average age of 79 years, and 59% were female (Table 1). Approximately 60% of cohort 1 subjects in each dose group had been previously treated for AMD. The types of previous treatment were similar across dose groups and included photodynamic therapy (33%), intravitreal pegaptanib sodium (30%), intravitreal triamcinolone acetonide (17%), and laser photocoagulation (10%). Investigating physicians elected to use the VA plus OCT retreatment criterion for approximately 81% of the subjects in each dose group.

Previously treated and treatment-naïve subjects had similar baseline ocular characteristics, with the exception that previously treated subjects had a longer time since first diagnosis and lower baseline VA (Table 2). Approximately 18% of cohort 1 subjects in each dose group discontinued the study before the month 12 visit (Table 3). Baseline ocular characteristics of subjects who com-

Table 1. Subject Baseline Characteristics

Characteristic	Cohort 1		Cohort 2
	0.3 mg (n = 1169)	*0.5 mg (n = 1209)*	*0.5 mg (n = 1922)*
Age (yrs)			
Mean ± SD	78.7±7.6	78.7±8.6	78.7±8.1
Range	51–97	52–101	45–99
Sex			
Female	59.9	58.1	61.6
Race			
Caucasian	96.6	97.1	96.2
AMD treatment history			
Treatment naïve	39.5	40.5	—
Previously treated	60.5	59.5	—
Retreatment criteria			
VA	19.3	18.4	—
VA plus OCT	80.7	81.6	—
Systolic BP			
Mean ± SD	137.4±17.3	137.8±18.0	—
Range	90–213	80–220	—
Diastolic BP			
Mean ± SD	76.2±9.7	77.0±9.7	—
Range	48–118	48–110	—

AMD = age-related macular degeneration; BP = blood pressure; OCT = optical coherence tomography; SD = standard deviation; VA = visual acuity.
Values are percentages except where otherwise noted.

Table 2. Baseline Ocular Characteristics

	Cohort 1				Cohort 2
	Treatment Naive		Previously Treated		
	0.3 mg (n = 462)	0.5 mg (n = 490)	0.3 mg (n = 707)	0.5 mg (n = 719)	0.5 mg (n = 1922)
Age at diagnosis (yrs)	79.9±7.9	75.8±8.0	79.9±7.5	79.9±7.5	—
Time since diagnosis (yrs)	0.3±1.4	0.3±0.7	1.4±2.0	1.3±1.7	—
CNV type (%)					
Predominantly classic	32.0	29.4	30.6	31.7	—
Minimally classic	19.7	20.2	26.2	23.5	—
Occult without classic	45.5	48.6	38.6	40.6	—
VA					
ETDRS letters	55.0±12.5	48.9±13.8	53.8±13.8	50.0±14.3	—
Snellen					
Median	20/80	20/80	20/100	20/100	20/100
20/200 or worse (%)	12.2	15.0	22.9	23.0	39
Central foveal thickness (μm)	312±104	322±116	315±113	310±113	—
Intraocular pressure (mmHg)	15.3±3.2	15.3±3.2	15.7±3.3	15.4±3.4	—

CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; VA = visual acuity.
Values are mean ± standard deviation except where otherwise noted.

pleted the study and those who discontinued were similar. All cohort 1 subjects received their assigned dose of ranibizumab on day 0, and approximately 96% of cohort 1 subjects received their assigned dose at months 1 and 2 (Fig 2). Cohort 1 subjects received an average of 4.6 injections during the 12-month study (the protocol required 3 initial injections). The average number of visits was 8.8 (the protocol required 7 scheduled visits). During months that visits were not scheduled (i.e., months 4, 5, 7, 8, 10, and 11), approximately 40% of the subjects made unscheduled visits, and approximately 16% of those subjects received an injection of ranibizumab at the unscheduled visit (relative to the number of subjects remaining in the study that month) (Fig 2).

From March 2006 to June 30, 2006, 1922 cohort 2 subjects were enrolled at 104 US centers and received 0.5 mg intravitreal ranibizumab (Table 1). Approximately 50% of cohort 2 subjects discontinued the study before the month 12 visit (Table 3). All cohort 2 subjects received the protocol-required injection on day 0 and received an average of 3.6 injections during the 12-month study (the protocol required 1 injection). The average number of visits for cohort 2 subjects was 4.9 (the protocol required 3 scheduled visits). During months that visits were not required (i.e., all but months 6 and 12), the percentage of subjects who remained in the study that made unscheduled visits ranged from 65% at month 2 to 17.4% at month 11. The percentage of subjects receiving injections ranged from 64% at month 2 to 16.5% at month 11.

Table 3. Reasons for Discontinuation

	Cohort 1		Cohort 2
	0.3 mg (n = 1169)	0.5 mg (n = 1209)	0.5 mg (n = 1922)
Discontinued early (%)	18.6	18.0	50.1
Reason for early discontinuation (%)			
Death	1.7	2.3	1.5
Adverse event	2.6	2.2	1.8
Loss to follow-up	0.7	0.9	2.0
Subject decision	6.7	5.8	29.0
Physician decision	3.4	2.8	9.4
Sponsor decision	0.2	0.1	0.3
Subject noncompliance	0.6	0.9	0.9
Subject's condition mandated other therapeutic intervention	2.7	3.1	5.3
Reason not provided	0.1	0	0

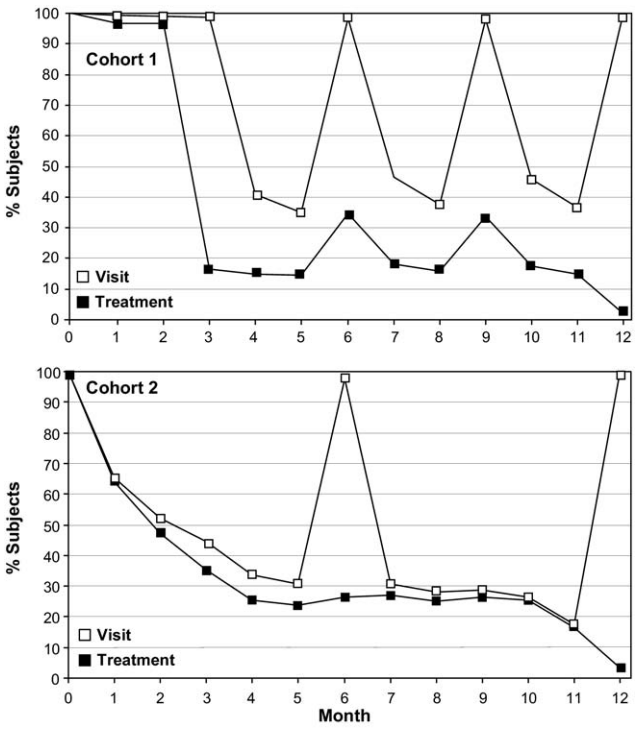

Figure 2. Visits and treatment. The percentage of cohort 1 (upper) and cohort 2 (lower) patients making visits and receiving ranibizumab treatment during each month of the 12-month study are shown. Cohort 1 visits were scheduled for day 0 and months 1, 2, 3, 6, 9, and 12. Cohort 2 visits were scheduled for day 0 and months 6 and 12. Data from cohort 1 0.3 and 0.5 mg dose groups are combined. Values are based on the percentage of subjects remaining in the study at each time point. Treatment received at month 12 was in violation of the protocol.

Table 4. Key Ocular Serious Adverse Events

Event, %	Cohort 1		Cohort 2
	0.3 mg (n = 1169)	*0.5 mg (n = 1209)*	*0.5 mg (n = 1922)*
Presumed endophthalmitis*	0.2	0.4	0.1
Uveitis	0.1	0.2	0
Retinal detachment	0.1	0	0.1
Retinal tear	0	0.1	0
Retinal hemorrhage	0.9	0.9	0.3
Detachment of retinal pigment epithelium	0	0.2	0.1
Vitreous hemorrhage	0.3	0.1	0.2
Cataract	0.1	0.1	0.1

*Includes 2 cases of uveitis and 1 case of iridocyclitis that were treated with antibiotics.

Safety

Ocular safety. The rates of individual key ocular SAEs in cohort 1 were <1% and similar across dose groups (Table 4). Two subjects (0.2%) in the 0.3 mg group and 5 subjects (0.4%) in the 0.5 mg group developed endophthalmitis or presumed endophthalmitis (i.e., ocular infection treated with antibiotics). One subject in each cohort 1 dose group had a serious cataract event. The rates of individual key ocular SAEs in cohort 2 were <1%. One cohort 2 subject developed endophthalmitis, and 1 subject had a serious cataract event (Table 4).

The incidence of ocular inflammation AEs, including iritis, uveitis, vitritis, and iridocyclitis, was 1.0% in the 0.3 mg group, 1.5% in the 0.5 mg group, and 0.5% in cohort 2. The overall incidence of cataract AEs was 5.4% in the 0.3 mg group, 6.0% in the 0.5 mg group, and 2.8% in cohort 2, and was similar when broken down by nuclear, subcapsular, and cortical subtypes.

Nonocular safety. The rates of key nonocular SAEs were similar across cohort 1 dose groups (Fig 3; Table 5). Nonvascular death, stroke, and hemorrhage rates were numerically higher in the 0.5 mg group. Eight subjects (0.7%) in the 0.3 mg group and 15 subjects (1.2%) in the 0.5 mg group had a stroke during the

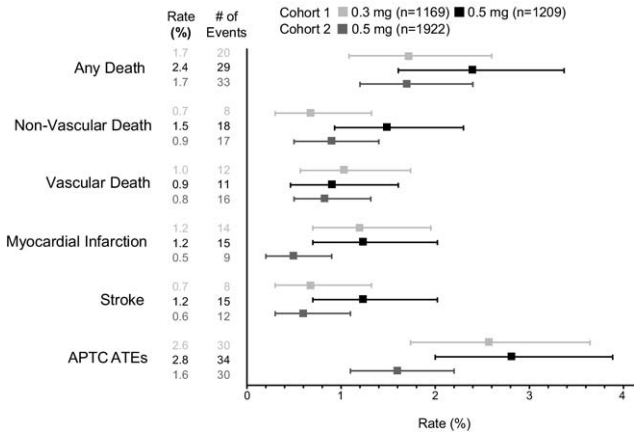

Figure 3. Key nonocular SAEs. The rates of individual events are depicted as point estimates with 2-sided Blyth-Still-Casella 95% confidence intervals. Antiplatelet Trialists' Collaboration ATEs include vascular deaths and deaths due to unknown cause, nonfatal MI, and nonfatal stroke. APTC = Antiplatelet Trialists' Collaboration; ATE = arterial thromboembolic event; SAE = serious adverse events.

Table 5. Nonocular Adverse Events Potentially Related to Anti-Vascular Endothelial Growth Factor Therapy

Classification, %	Cohort 1		Cohort 2
	0.3 mg (n = 1169)	*0.5 mg (n = 1209)*	*0.5 mg (n = 1922)*
Arterial thromboembolic events			
All	3.8	4.1	2.4
Serious	2.5	3.1	1.6
Hypertension			
All	9.0	10.3	3.0
Serious	0.1	0.1	0
Nonocular hemorrhage			
All	2.9	3.1	1.4
Serious	0.9	1.5	0.6
Proteinuria			
All	0.1	0	0
Serious	0	0	0
Other			
All	0.7	0.4	0.1
Serious	0.3	0.2	0.1

VEGF = vascular endothelial growth factor.

12-month study period. The incidence of MI and Antiplatelet Trialists' Collaboration (APTC)[3] arterial thromboembolic events (ATEs), which include vascular death and death of unknown cause, nonfatal MI, and nonfatal cardiovascular accidents, were similar across cohort 1 dose groups.

Rates of key nonocular SAEs in cohort 2 were generally lower than those in cohort 1, which may be a result of underreporting because of the large number of cohort 2 subjects who discontinued. The incidence of nonocular AEs potentially related to anti-VEGF therapy was low and comparable across cohorts and dose groups.

Prior stroke, history of arrhythmias, and history of congestive heart failure were significant risk factors for stroke (Fig 4). Although the numbers were small, there was a nonstatistically significant trend toward higher incidence of stroke in the cohort 1 0.5 mg group subjects with a history of stroke. Seven of the 73 subjects (9.6%) with a history of stroke in the 0.5 mg group experienced a stroke during the study compared with 2 of the 73 subjects (2.7%) with a history of stroke in the 0.3 mg group. None of the cohort 2 subjects with a history of stroke experienced a stroke during the study (Fig 4).

Twenty subjects (1.7%) in the cohort 1 0.3 mg group, 29 subjects (2.4%) in the cohort 1 0.5 mg group, and 33 subjects (1.7%) in cohort 2 died during the 12-month study (Table 6). The number of vascular deaths and deaths due to unknown cause did not differ across cohorts or dose groups.

Efficacy

Cohort 1 efficacy results were stratified by dose and previous treatment for AMD. For all groups, study eye VA increased with 3 loading doses of ranibizumab (day 0, month 1, month 3) (Fig 5). At month 3, treatment-naïve subjects in the 0.3 mg group had gained an average of 5.8 VA letters and those in the 0.5 mg group had gained an average of 7.0 VA letters. From months 3 to 12, with protocol-defined retreatment, VA tended to decrease. At month 12, treatment-naïve subjects in the 0.3 mg group had gained an average of 0.5 VA letters and those in the 0.5 mg group had gained an average of 2.3 letters. A similar pattern was observed for previ-

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