



# EyeQ Report<sup>TM</sup>

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Written by Michael Lachman,  
unless otherwise noted

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## ARVO 2006: Avastin Comes Home to South Florida for a Victory Lap

**It was just one year ago, at ARVO 2005 in Fort Lauderdale, that outcomes for Avastin for neovascular AMD were first reported.** The use of systemic Avastin for AMD had been pioneered in the SANA study by the retina specialists at the Bascom Palmer Eye Institute at "The U," just thirty miles down the road from the ARVO venue. At that time, ophthalmic experience with Avastin was extremely limited but very encouraging. Patient numbers were small and the follow-up period was limited (only nine patients had reached the three-month

point in the SANA study), and the administration was systemic instead of intravitreal. Despite the small numbers and intravenous infusion, patients showed significant improvement in visual acuity at three months and in central retinal thickness as early as one week post-infusion. However, there remained concern over the elevated risk of thromboembolic events that had been observed with systemic use of Avastin for colon cancer.

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## Lucentis: Still Strong at Two Years and Effective in Less Frequent Dosing

**Two year efficacy and safety results from the MARINA trial were reported last week at ARVO, and did not disappoint.** MARINA is a 716-patient randomized, controlled Phase III study of Lucentis for minimally classic or occult neovascular wet AMD. Dosages of 0.3 mg and 0.5 mg were randomized 1:1:1 against sham treatment. Patients received monthly injections over the 24 months of the study. It was announced at ASRS last July that Lucentis had met the primary efficacy endpoint: maintenance of vision, defined as loss of <15 letters (3 lines) of visual acuity at 12 months.

**On May 2, Jeffrey S. Heier, MD of Boston reported impressive two-year efficacy results from MARINA.**

Compliance at 24 months was good, with 89% of treated patients and 80% of sham patients available for 24-month examination. Treated patients received an average of 22 injections out of a possible

24. As shown in the table on Page 5, Lucentis continued to perform exceptionally well during the second year of treatment on all visual acuity metrics, further distancing itself from sham treatment. With regard to "response rate," or the relative increase in the percentage of patients "maintaining" vision in-line with the primary endpoint, Lucentis improved from 53% to 72% during the second year. In terms of mean change in visual acuity versus sham treatment, the Lucentis-treated eyes gained an additional 3-4 letters during the second year, for a net treatment effect of 20-21 letters (four lines) after two years.

During MARINA, investigators were allowed to offer Visudyne photodynamic therapy (PDT) or Macugen to patients at their discretion if they met certain criteria regarding disease progression.

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Avastin from Page 1

Last spring, Philip J. Rosenfeld, MD, PhD and his colleagues at Bascom Palmer looked at the encouraging preliminary outcomes for systemic Avastin and for intravitreal Lucentis, recognized the commercial availability of Avastin and the 400x lower dose if administered intravitreally versus systemically, and took a leap of faith. They started injecting Avastin intravitreally (and very much off-label) for neovascular AMD, and reported their very favorable early clinical experience at the ASRS meeting last July in Montreal. The low cost of the drug, about \$17-50 per injection in quantities appropriate for intravitreal use, lowered barriers to adoption in the US and internationally. By the winter, intravitreal Avastin had become the global *de facto* standard of care for wet AMD.



Last week at ARVO 2006, Dr. Rosenfeld summarized the excellent outcomes seen so far with intravitreal Avastin in neovascular AMD patients: average visual acuity from about 20/200 to 20/100, 44% of patients gaining 3 or more lines of visual acuity, and decrease of retinal thickness of about 100µm. As with Lucentis, the duration of effect is variable. Regarding the medical-legal aspects of off-label Avastin use, Rosenfeld argues that it is legal, ethical, and the logical application of scientific and clinical knowledge to patient care. Another prominent retina specialist pointed out that, given all of the investigator-sponsored research that is being conducted and reported for Avastin in retinal diseases other than AMD, Lucentis will be “more off-label” than Avastin for these non-AMD applications.

A web-based safety survey of intravitreal Avastin use, led by Anne Fung, MD of San Francisco, has compiled data from 7,113 injections since May 2005. These injections were performed in 5,228 patients treated in 70 centers in 12 countries. As a voluntary survey, it likely represents only a fraction of the actual number of intravitreal Avastin injections that have been performed around the world over

the past year. A retina specialist from Germany told us that there have been over 5,000 Avastin injections in his country alone since December. Regarding the safety database itself, as a voluntary, self-reported survey it is far from perfect, but results so far are encouraging, with key adverse events (treatment-related, ocular, and systemic) all occurring at rates of 0.2% or lower.

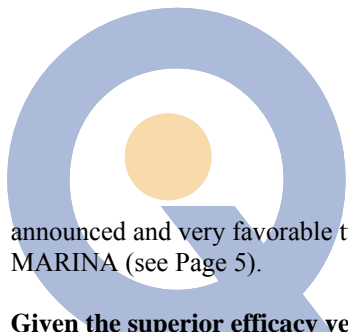
**With off-label use of Avastin growing and FDA approval of Lucentis likely less than two months away**, hot topics of discussion at ARVO were various pricing scenarios for Lucentis and what would happen to Avastin use following FDA approval of Lucentis.

**Key Question #1: How will Lucentis be priced in the US?**

Eyetech set a high bar with its \$995 per dose pricing of Macugen, resulting in an annual cost of about \$6,000 per year based on six injections (or about \$8,000 per year based on the labeled six-week interval). Lucentis has proven to be significantly more effective, and should be able to command a higher price. Although the pivotal MARINA and ANCHOR studies of Lucentis featured monthly dosing, Bascom Palmer’s PrONTO study (see Page 6) strongly suggests that less frequent dosing (5-6 injections per year instead of 12-13) is equally effective. Results from Genentech’s Phase IIIb PIER study, which examines a less frequent dosing regimen of Lucentis that also results in six injections during the first year of treatment, should be available to the FDA this month, in advance of the June 30 FDA action date. As such, it is possible that this less frequent dosing regimen could be incorporated into the Lucentis label. The significance of this from a pricing standpoint is that Genentech would be able to support per-dose pricing for Lucentis based upon an average of six treatments during the first year, not 13.

**We also heard at ARVO that Genentech is pursuing the 0.5mg dose for Lucentis in the US, instead of the 0.3mg dose.** After Genentech reported ANCHOR trial results in January, which raised the possibility of elevated cardiovascular risk for the higher dose, comments from management suggested a bias toward the lower dose despite its somewhat lower efficacy. This would have been the more conservative path, one that the company characterized as having a “low likelihood of being wrong.” We have heard that since that time, the company and the FDA have gotten comfortable with the safety profile of the more efficacious 0.5mg dose, a conclusion supported by the recently

Continued on next page



announced and very favorable two-year safety results from MARINA (see Page 5).

**Given the superior efficacy versus Macugen**, an average of six treatments per year, and high dose formulation, we would not be surprised to see Lucentis priced in the US in a range of \$2,000-3,000 per dose. Pricing below \$1,500 per dose seems highly unlikely.

## Key Question #2: What Will Happen to Avastin Use Once Lucentis is FDA-Approved?

**Because Avastin is formulated and priced for intravenous infusion for the treatment of colorectal cancer, it is very inexpensive in the small quantities used for intravitreal injection** (25-30 syringes per vial of Avastin, costing \$50 or less per dose). The fact that Medicare is not currently providing reimbursement for the off-label drug is a relatively small annoyance to retina specialists; the lack of reimbursement for the injection, which would normally be over \$200, is a bigger deal. In some cases, private insurance is covering the Avastin injections or patients are paying out-of-pocket (generally \$300-500 for the drug and injection). In other cases, retina specialists are “eating” the cost, in the name of providing the best available therapy for their neovascular AMD patients.

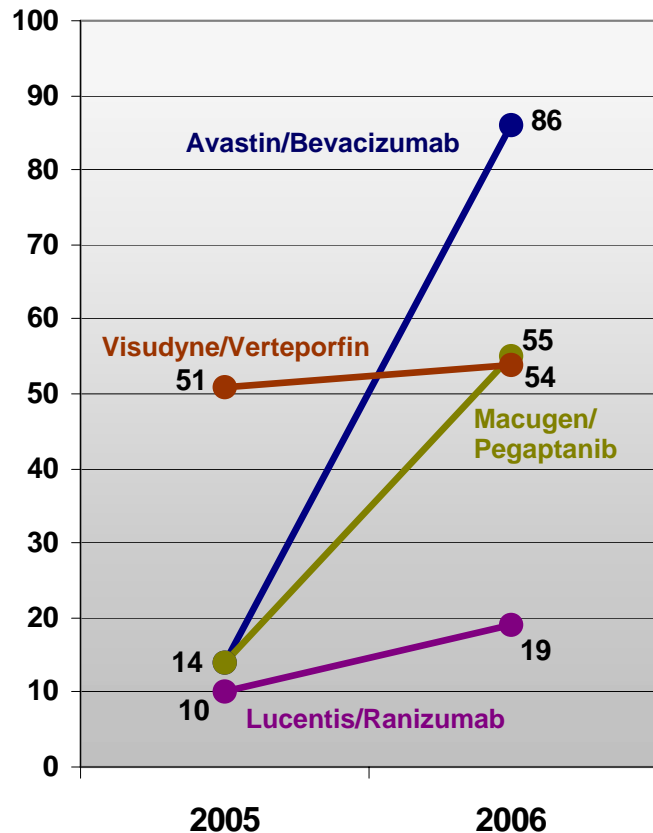
**Once FDA-approved, despite its inevitably much higher cost, Lucentis (drug and injection) will be reimbursed by Medicare for the treatment of neovascular AMD.** Because of reimbursement, as well as the medical-legal benefits of using an on-label drug when possible, Lucentis will likely be used for patients that are fully insured (either private insurance or Medicare plus supplemental insurance to cover the 20% co-pay). Avastin will likely still be used for uninsured or partially-insured AMD patients in the US that cannot afford Lucentis, as well as for the many off-label indications that are being treated with intravitreal Avastin (see table on Page 4). Internationally, where healthcare spending is more tightly constrained, Avastin will be much more difficult to displace. Longer term, it is likely that organizations such as CMS and NIH will initiate randomized, controlled studies to validate the safety and efficacy of intravitreal Avastin, given the enormous potential savings to the Medicare system.

## If Avastin is So Effective Against Neovascular AMD, Why was Lucentis Developed?

**Avastin (bevacizumab), developed by Genentech, is a humanized anti-VEGF antibody that received FDA approval in February 2004 for use as a first-line treatment for metastatic colorectal cancer.** Lucentis (ranibizumab), an antibody fragment derived from the same molecule, is much smaller (about 1/3 the molecular weight of

Avastin). Based upon experiments conducted with Herceptin, a monoclonal antibody of similar size as Avastin, Genentech theorized that Avastin was too large a molecule to penetrate the retina and retinal pigment epithelium. As demonstrated by several papers and posters at ARVO 2006, this theory turned out to be wrong. Researchers are consistently reporting rapid and sustained full-thickness penetration of Avastin into the retina

## Number of ARVO Abstract References to AMD Treatment Modalities, 2005-2006



Notes: All 14 references to Avastin in the 2005 abstracts described systemic, not intravitreal, administration. Total ARVO abstracts (posters, papers, symposia, workshops): 6,209 in 2005; 6,373 in 2006.

## Highlights from ARVO Papers and Posters on Intravitreal Avastin for Retinal Disease

**At an ARVO paper session, Richard Spaide, MD reported on the first three months of experience of his New York City practice with intravitreal Avastin for CNV.** They used a 1.25mg dose, at a unit cost of \$16, and

Continued on next page



injected monthly. The practice started using Avastin on “salvage cases” before moving on to “virgin eyes,” and about 70% of the 266 patients treated had previously failed on other forms of treatment (PDT, Macugen). Over the first three months of follow-up, visual acuity gradually improved, from a mean baseline level of 20/184 to a 3-month mean of 20/109. 38% of patients had improved visual acuity, while only 5% got worse. Over the first two months, central macular thickness decreased by nearly 100µm, from 340 to 244µm.

**In another paper, Dante Pieramici, MD and Robert Avery, MD of Santa Barbara reported on their initial**

#### **Sampling of Ocular Conditions Under Investigation for Treatment with Intravitreal Avastin, and Countries Represented with Avastin Research at ARVO 2006**

CNV secondary to AMD (all subtypes)  
Salvage therapy for AMD (post-Macugen or PDT)  
CNV secondary to pathologic myopia  
Idiopathic subfoveal CNV  
Corneal angiogenesis/neovascularization  
Ocular disorders involving fibroblast proliferation  
Central retinal vein occlusion  
Branch retinal vein occlusion  
Pre-surgical treatment to reduce bleeding before retinal surg.  
Treatment of CNV in patients with angioid streaks  
Diabetic macular edema  
Diabetic retinopathy (proliferative and non-proliferative)  
Neovascular glaucoma  
Rubiosis (iris neovascularization)

Countries:  
United States, Austria, Brazil, Colombia, Germany, Israel, Japan, Mexico, Peru, Venezuela

Source: ARVO 2006 Abstracts

**experience with intravitreal Avastin for AMD.** In this retrospective review of 81 eyes, nearly 80% had already failed on other treatments. A mean of 3.3 Avastin injections were required over a six month period. A biologic effect was noted in all angiographic subtypes, with resolution of edema as soon as six hours post-injection. Mean visual acuity improved from 20/200 to about 20/80-20/100 at the 1-month and 6-month follow-ups. The mean reduction in retinal thickness was 90µm, most of which was observed by the end of the first month.

**Avastin is now being used experimentally for a wide variety of retinal conditions.** Reports from around the world describing these initial clinical experiences with Avastin dominated the scientific program at ARVO 2006. Our search of the ARVO abstract database turned up 86 posters and papers referencing Avastin/bevacizumab, versus just 14 last year, all 14 of which described systemic use (see chart on Page 3). Some of the ocular conditions for which experience with Avastin was reported at ARVO 2006, and the countries of origin for this research, are listed in the table at left. To detail all of these research results here is beyond the scope of this report, but with few exceptions, intravitreal Avastin led to one or more of the following outcomes: (1) improved visual acuity, (2) decreased central retinal thickness and vascular leakage, and (3) favorable safety profile.

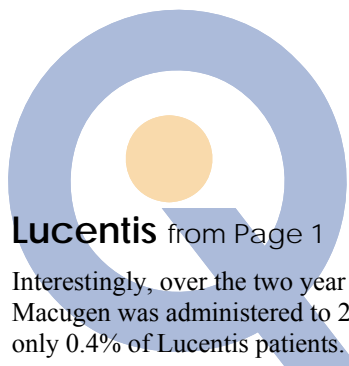
**Although clinical experience with intravitreal Avastin is clearly in its earliest stages, there appears to be no “red flag” or “smoking gun” that would suggest an underlying issue regarding safety or efficacy.** Over the past several years, intravitreal Kenalog (triamcinolone) has become the default “wonder drug” used to treat a variety of retinal conditions, including AMD (in combination with PDT), macular edema, and retinal vein occlusion, despite known risks of cataract formation and elevated IOP. Avastin has quickly taken over this role from triamcinolone, with apparent advantages in both safety and efficacy. **Q**

#### **Presbyopia Takes a Holiday, but Not a Florida Vacation**

After all of the attention showered upon new technologies to treat presbyopia at the ASCRS in March and at AAO last fall, the lack of focus on this topic at ARVO was remarkable. Of the nearly 6,400 posters and papers presented at ARVO, by our count only 15 dealt with presbyopia products and technologies, including multifocal IOLs (5), accommodating IOLs (3), corneal inlays (3), CK (2), multifocal LASIK (1) and scleral implants (1).

#### **Correction**

In our April 4 issue (EyeQ Report No. 5), we incorrectly identified the Lenstec Tetraflex Accommodating IOL as the “Kelman” lens... not once, but four times. It is actually the “Kellan” lens, developed by Robert E. Kellan, MD of Boston, not by the late Charles D. Kelman, MD, inventor of phacoemulsification. Our apologies to Dr. Kellan.



## Lucentis from Page 1

Interestingly, over the two year study period, PDT or Macugen was administered to 21% of sham patients but to only 0.4% of Lucentis patients.

**Separately, Dr. Heier reported on anatomic outcomes from MARINA and ANCHOR, quantifying some of the physiologic changes behind the improvements in visual acuity.** In MARINA, the mean area of CNV leakage increased by 1.2 DA in untreated (sham) eyes, and in ANCHOR, this metric increased by 0.3 DA for PDT-treated eyes. In both studies, the mean area of CNV leakage decreased by about 2 DA in eyes treated with Lucentis. With regard to mean retinal thickness, in MARINA, sham-treated eyes decreased by 15µm and Lucentis-treated eyes decreased by 123µm. In ANCHOR, PDT-treated eyes decreased by 87µm and Lucentis-treated eyes decreased by 190µm. Dr. Heier noted that there are 48 investigator-sponsored trials in

the works for Lucentis: 13 active trials, 12 approved protocols, and 23 approved concepts.

**On May 3, Joan W. Miller, MD of Harvard Medical School reported satisfactory two-year safety results from MARINA.** On key safety metrics, Lucentis was no worse than sham treatment, and the two Lucentis dosages were similar to each other. With regard to serious ocular adverse events, endophthalmitis occurred in 1.0% of patients through 24 months, and uveitis occurred in 1.3% of patients. These are cumulative rates per patient over 22 injections, not rates per injection; as such, it is not surprising that these complication rates were roughly double the cumulative rates at 12 months.

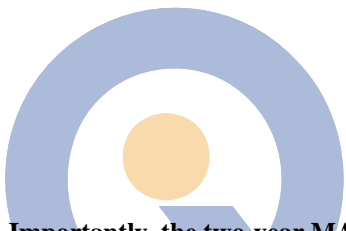
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### Lucentis MARINA Study: Key Efficacy and Safety Results at 12 and 24 Months

	12 Months			24 Months		
	Sham	0.3mg	0.5mg	Sham	0.3mg	0.5mg
<b>Efficacy Endpoints</b>						
	<b>Primary Endpoint:</b>					
Vision Maintenance: % Losing <15 Letters	62%	95%	95%	53%	92%	90%
Vision Maintenance Response Rate: Treated/Sham	N/A	+53%	+53%	N/A	+74%	+70%
% Gaining ≥15 Letters	5%	25%	34%	4%	26%	33%
% Gaining ≥30 Letters	0%	3%	4%	0%	5%	6%
% Losing ≥30 Letters	14%	1%	1%	23%	3%	3%
% Gaining =0 Letters	29%	75%	71%	25%	71%	70%
Mean Change in VA (Letters)	-10.4	+6.5	+7.2	-14.9	+5.4	+6.6
Mean Change in VA vs. Sham	N/A	+16.9	+17.6	N/A	+20.3	+21.4
<b>Safety Endpoints</b>						
Presumed Endophthalmitis (Cumulative, per Patient)	0%	0.4%	0.8%	0%	0.8%	1.3%
Uveitis (Cumulative, per Patient)	0%	0.8%	0.4%	0%	1.3%	1.3%
Cataract Formation	10.6%	8.0%	9.2%	15.7%	15.5%	15.5%
In-Study All-Cause Mortality				2.5%	2.1%	2.5%
Non-Ocular Hemorrhagic Events				5.5%	9.2%	8.8%
Hypertension				16.1%	17.2%	16.3%
Tot. Arterial Thromboembolic Events	0.8%	1.7%	2.1%	3.8%	4.6%	4.6%

Sources: Jeffrey S. Heier, MD and Joan W. Miller, MD - ARVO 2006; Genentech company reports





**Importantly, the two-year MARINA safety data is very favorable with respect to key non-ocular adverse events, particularly cardiovascular.** In the previously reported 12 month results of MARINA, the rate of arterial thromboembolic events was higher in the two Lucentis groups (1.7% for 0.3mg and 2.1% for 0.5mg) than in the sham group (0.8%). Recall that when Genentech announced the results of the ANCHOR study in January, the company reported that the combined rate of stroke and myocardial infarction in both ANCHOR and MARINA with monthly dosing was similar in the control and the 0.3 mg Lucentis arms (1.3% and 1.6% respectively) and slightly higher in the 0.5 mg Lucentis arm (2.9%). At that time, Genentech seemed to be leaning toward submitting for FDA approval of the 0.3mg dose, because it was only slightly less efficacious than the 0.5mg dose and would avoid many of the questions regarding cardiovascular safety. At the same time, Pfizer/OSI/Eyetech's competitive marketing strategy for Macugen seemed to be hanging by the thin thread of Lucentis cardiovascular risk. At ARVO 2006, this thin thread broke.

**At 24 month follow-up in MARINA,** the rates of arterial thromboembolic events (including stroke, myocardial infarction, and vascular deaths) were similar for the sham group (3.8%) and each of the two Lucentis groups (4.6%). All-cause mortality rates were also similar for the sham (2.5%) and treated (2.3%) groups. Hypertension was observed in 16% of sham patients and 17% of treated patients. The rate of non-ocular hemorrhagic adverse events was slightly higher in treated patients (9%) than in sham patients (5.5%). There was a low rate of systemic immunoreactivity to treatment observed at 24 months (about 5% versus about 1% for untreated patients), and no correlation between immunoreactivity and safety or efficacy outcomes.

**David M. Brown, MD of Houston reported on subgroup analysis of the 12-month results of the ANCHOR trial, which compared Lucentis to PDT.** According to Dr. Brown, this analysis was used to determine if there is a subgroup of patients for which PDT "has a chance" to outperform Lucentis. There was not such a subgroup identified; Lucentis outperformed PDT in all subgroups based on age, baseline visual acuity, CNV lesion size, and lesion type.

## Less Frequent Dosing of Lucentis Appears Very Promising

**Philip Rosenfeld, MD, PhD presented the initial experience with less frequent Lucentis dosing from the single-site (Bascom Palmer), open-label PrONTO study.**

During the Phase I/II extension studies of Lucentis, it was observed that once the scheduled monthly injections stopped, the need for re-injection varied from patient to patient. It was also observed that cysts were visible on optical coherence tomography (OCT) before leakage became evident on fluorescein angiography (FA) or vision declined. In PrONTO, three initial monthly injections of Lucentis (0.5mg) were administered, followed by additional injections based on specific criteria (increase in retinal thickness, visual decline, new CNV leakage, or fluid observed on OCT). During the study, OCT examination was the primary driver of additional injections, as opposed to FA or visual exam. As Dr. Rosenfeld put it, one of the lessons of PrONTO is that "little cysts become big cysts if not treated."

**Forty patients were enrolled in PrONTO, and followed out to 12 months.** As observed in the earlier extension trials, the need for re-treatment was unpredictable for individual patients. The mean number of injections per patient over the first year was 5.5 (the initial three injections plus 2.5 additional). The median number of injections was 5. About 38% of patients received 0-1 additional injections beyond the initial three, and only 5% of patients required monthly injections over the first year, as administered in MARINA and ANCHOR. The investigators are looking at baseline lesion characteristics to see if they can predict up-front which lesions will require specific levels of re-treatment.

**Visual outcomes in PrONTO were consistent with the MARINA and ANCHOR studies.** By month 12, patients had gained an average of 9.3 letters of vision, in-line with the 7-11 letter gain reported at 12 months in MARINA and ANCHOR for the 0.5mg dose. Three or more lines of visual improvement was noted in 35% of patients, and only 18% lost letters of vision. Central retinal thickness decreased by an average of 178µm. There was complete resolution of retinal cysts and sub-retinal fluid in 72% of eyes after one month and 95% by three months. **Q**





## AMD Roundup: Visudyne/PDT, Macugen, and VEGF Trap

**Neither of the currently approved treatments for AMD – Visudyne/PDT or Macugen, attracted a lot of positive attention at ARVO.** Once Lucentis is approved, Visudyne is likely to be used by a subset of retina specialists, primarily for patients that are not responding to either Lucentis or Avastin. We have seen no evidence so far that Visudyne/PDT contributes incrementally to outcomes achieved with either Lucentis or Avastin. With regard to Macugen, some of the papers and posters at ARVO supported its efficacy, with outcomes in-line with or superior to those from the pivotal VISION study. Other presentations detailed efficacy results that fell short of this mark. Suggestions that Macugen could find a niche as maintenance therapy following initial treatment with Lucentis do not make sense to us, given the strong performance of Lucentis as maintenance therapy (with infrequent, as-needed dosing) in the PrONTO study. Also, following the release of 24 month safety data for Lucentis from MARINA, the cardiovascular safety argument supporting Macugen is losing steam. Consensus is building among retina specialists that Macugen has minimal efficacy, and will not have a prominent place in AMD treatment alongside Lucentis and Avastin.

### VEGF Trap Delivers Encouraging Phase I Results in AMD

**With Lucentis and Avastin having raised the bar so meaningfully, it can be difficult to get excited about early stage treatments in the clinic for neovascular AMD.** However, at ARVO, Regeneron Pharmaceuticals reported favorable results in its Phase I dose-escalation study of intravitreal VEGF Trap. This molecule is a potent anti-angiogenic agent that binds and blocks the action of all VEGF-A isoforms and placental growth factor. In the study, 21 patients received a single injection of one of six doses of VEGF Trap, from 0.05mg to 4mg, and were monitored for 12 weeks (six-week results reported).

**There were no systemic serious adverse events and no reports of endophthalmitis or inflammation.** Visual acuity improved by a mean of 4.8 letters (1 line) for all patients, and by 13.5 letters (2.7 lines) for the two highest dose groups. In these highest dose groups, 3 of 6 patients achieved gains of  $\geq 3$  lines of visual acuity. There was a rapid decrease in median central retinal thickness that lasted, on average, for the entire six week observation period. For the three highest dose levels, the median decrease in retinal thickness was on the order of 100 $\mu$ m. Based on the Phase I results, Regeneron announced the start of a 150 patient, 12 week, Phase II trial of VEGF Trap in wet AMD. The trial is designed to evaluate safety and efficacy of multiple doses of VEGF Trap using different doses and different dosing regimens. **Q**



### Suggestion for 2007 ARVO Poster Topic

**If anyone is looking for a burning question to research for next year's ARVO, here's an idea:** Why did the Broward County Convention Center give its two largest ballrooms, which are located on opposite ends of the building, practically the same name? ("Floridian" and "Grand Floridian," see above.) Were they trying to be funny? Did they run out of available names? A few suggestions: Fort Lauderdale Ballroom? Dolphin Ballroom? Rosenfeld Ballroom?

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