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By Lynne Peterson

Quick Pulse

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Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA'S DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEETING ON EYETECH'S MACUGEN FOR WET AMD

Rockville, Maryland
August 27, 2004

Eyetech and its marketing partner, Pfizer, are seeking FDA approval of Macugen (pegaptanib sodium by intravitreal injection) for the treatment of all subgroups of wet (neovascular) age-related macular degeneration (ARMD/AMD). Macugen is a vascular endothelial growth factor inhibitor (anti-VEGF), and dose being requested is 0.3 mg every six weeks by intravitreal injection. Currently, there is only one FDA-approved AMD treatment – photodynamic therapy (PDT) with QLT's Visudyne (verteporfin). The FDA's Dermatologic and Ophthalmic Drugs Advisory Committee gave Macugen a very positive review, finishing its deliberations well ahead of schedule, and it now looks very likely that the FDA will approve Macugen when manufacturing issues are resolved.

In fact, the meeting was basically a cakewalk for Eyetech. The FDA and the panel seemed to agree that Macugen has at least a 15% treatment effect vs. sham and that it is safe for up to two years. The eight voting members of the committee included: three retinal specialists, one refractive surgeon, one pediatric ophthalmologist, a statistician, a university IRB official, and a patient advocate. The industry representative (from Allergan) did not have a vote. A retinal specialist on the panel commented early in the deliberations, "I'm very impressed."

However, FDA officials emphasized that they are still in the preliminary stages of reviewing Macugen, which is being processed as a "rolling submission" or a Continuous Marketing Application Pilot 1 NDA submission. Eyetech officials said all the modules of the application have been submitted, though the FDA does not confirm submissions. The PDUFA date is December 17, 2004. The comments of the FDA reviewer and the panel's comments/votes seem to indicate that the clinical part of the application has passed muster. Another FDA official, asked about the clinical part of the application, said, "This is it."

There are still remaining issues that could delay approval but are unlikely to lead to a not-approvable letter. These issues include:

- **Manufacturing.** An FDA official said, "CMC issues need to be addressed."
- **Shelf life/stability.**
- **Packaging.** Can Macugen be put in a plastic syringe instead of a glass one?

Before this FDA Advisory Committee meeting, Eyetech had provided only a pooled analysis of one-year data from the two pivotal Phase II/III studies of Macugen, which made many people suspicious that there was something wrong with the data, a "smoking gun" that would make this product difficult if not

FDA Review of Macugen Efficacy Data

Measurement	Macugen 0.3 mg	Macugen 1.0 mg	Macugen 3.0 mg	Sham
International Study EOP1003				
Number of patients randomized and treated	151	155	153	153
Patients who discontinued treatment	11	13	17	12
Primary endpoint by LOCF: Responders (% of patients who lost <15 letters of visual acuity from baseline at 54 weeks)	73.2% p=.01	75.3% p=.002	69.7% p=.06	59.6%
Primary endpoint per protocol in observed cases only: Responders at 54 weeks	73.7% p=.01	75.5% p=.005	66.7%	58.6%
Responders by worst-case analysis*	68% p=.15	69% p=.11	60% Nss	61.5%
Secondary endpoint #1: % of patients gaining >15 lines of VA from baseline to 54 weeks	4% p=.93	6% p=.49	5% Nss	3%
Secondary endpoint #2: % of patients gaining 0 lines of VA from baseline to 54 weeks	33% p=.38	38% p=.08	39% Nss	28%
North American Study EOP1004				
Number of patients	144	146	143	145
Patients who discontinued treatment	12	17	20	11
Primary endpoint by LOCF: Responders (% of patients who lost <15 letters of visual acuity from baseline at 54 weeks)	67.4% p=.016	66.7% p=.032	61.9% p=.13	53.4%
Primary endpoint per protocol in observed cases only: Responders at 54 weeks	67.9% p=.0008	66.0% p=.06	57.4% p=.059	53.9%
Responders by worst-case analysis*	61.8% p=.27	60.5% p=.76	49.7% p=.36	58.8%
Secondary endpoint #1: % of patients gaining >15 lines of VA from baseline to 54 weeks	8% p=.005	7% p=.01	4% p=.04	1%
Secondary endpoint #2: % of patients gaining 0 lines of VA from baseline to 54 weeks	34% p=.0006	35% p=.002	23% p=.17	17%

*** In the worst case analysis, the FDA assumed all patients in the sham group with missing VA measurements were responders, and all patients in the Macugen group with missing VA measurements were non-responders.**

FDA Review of Macugen Safety in All Treated Patients

Measurement	Macugen 0.3 mg	Macugen 1.0 mg	Macugen 3.0 mg	Sham
Number of patients	295	304	367	298
Patients with at least one ophthalmic adverse event in the Study Eye	91%	90%	91%	85%
Patients with at least one serious adverse event	19%	17%	22%	15%
Patients with an adverse event causing treatment interruption/discontinuation	2%	2%	3%	2%
Endophthalmitis	2%	1%	1%	0
Eye pain	34%	32%	36%	29%
Punctate keratitis	33%	30%	33%	27%
Vitreous floaters	31%	35%	35%	8%
Vitreous opacities	19%	19%	19%	10%
Anterior chamber inflammation	16%	14%	14%	6%
Increase in intraocular pressure	14%	20%	26%	3%

Eyetech's Efficacy Analysis of Macugen vs. Sham

Measurement	Macugen 0.3 mg	Macugen 1.0 mg	Macugen 3.0 mg	Sham
Primary endpoint: **% patients losing <15 letters (3 lines) of vision at Week 54**				
Study EOP1003	p=.0105	p=.0035	N/A	N/A
Study EOP1004	p=.0031	p=.0273 (Nss) *	N/A	N/A
Study EOP1003 + Study EOP1004 combined	p<.0001	p=.0003	N/A	N/A
Pooled Efficacy Results				
Progression to VA ≤20/200	38% p<.0001	43% p=.001	N/A	56%
Severe vision loss (≥ 6 lines)	10%	8%	N/A	22%

*** Statistical significance is 0.025**

impossible to get approved. However, Eyetech and the FDA both finally released the separate data, and there was nothing in it that raised any real questions with the panel.

A. **EOP1003**, a two-year, ongoing, 622-patient study in Europe (60%), North America (14%), South America (7%), Israel (5%), and Australia (14%).

B. **EOP1004**, a 586-patient study in Canada and the U.S.

The briefing documents released the day before the panel meeting suggested several issues were likely to come up at the panel, but many of those proved to be non-issues and either were not discussed at all or talked about so briefly as to be inconsequential. These included:

- **The trial inclusion/exclusion criteria.**
- **The apparent lack of benefit in patients with light irises.**
- **An almost reverse dose response curve.**
- **A theoretical cardiac risk.** Eyetech had two prominent cardiologists and a urologist on hand to answer cardiac and renal questions if they arose, but they were never needed.
- **The frequency (every six weeks) of intravitreal injections.** A panel member did want to know if there was an implantable, slow-release device in development in case patients need to take Macugen long-term, and an Eyetech official responded, "We are working on other formulations and perhaps an implantable device…We would like to reduce the frequency (of injections). Study 1006, a PK study looking at the half-life in humans, is ongoing, and we are determining in the lab the relative inhibitory concentration when administered. With that data, if there is evidence we can dose less frequently, that is something we are willing to consider…but for now 0.3 mg every six weeks appears safe and effective."
- **Declining efficacy over time.**

The potential carcinogenicity of Macugen was not addressed in the briefing documents, but an Eyetech official said he believes the FDA has decided to grant the company a waiver of further testing. He is expecting to get the waiver in the mail soon. If the waiver is not granted, it now appears that the agency will most likely allow the testing to be done post-marketing.

The topics that did warrant discussion – but also mostly proved to be non-issues – included:

- **ETDRS measurements.** Eyetech measured ETDRS at 2 meters instead of 4 meters. Dr. Wiley Chambers, Deputy Director of Ophthalmics in the FDA's Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products, Office of Drug Evaluation V, Center for Drug Evaluation and Research (CDER), said, "The issue is the variability that occurs when you are measuring at 2 vs. 4 meters, and the potential for any bias if the patient is allowed to lean. If we strapped each patient down and didn't let them move, it wouldn't be an issue, but we don't do that. Seventeen inches is the equivalent of one line (of vision), and moving in your seat can do that. We don't have any reason to believe people are trying to bias the results, and people are aware of trying to keep patients from leaning, but studies have been shown greater variability at 2 meters. The overall impact on a particular trial is not known. The only way to know that is to measure at both 2 meters and 4 meters…The concern is that there may be a potential unmasking because of some of the adverse events, and then that may lead to differences. The issue is that there is more variability with measurements at 2 vs. 4 meters, though we don't have a good quantification on what that is."

Dr. Chambers admitted that the agency did not advise Eyetech before the start of the Macugen Phase III trials that 2 meters was not acceptable to the FDA. He explained, "We approved the use of ETDRS, and we assumed that meant 4 meters…We since learned that this is not the interpretation in the whole community…Some people call it ETDRS even though it doesn't meet the definition of ETDRS, which is 4 meters. We were aware of the difference after the trial started, and we commented about it…Then, the sponsor was faced with the question of making a protocol change (during the trial) or continuing with it as is." Eyetech's CEO said, "When we started the trial, our thought process was that Visudyne was done at 2 meters, in part because…Our thought was we could get more baseline readings…But the agency has good reasons for preferring 4 meters…There is no perfect distance. But if the masking is good, and if you make sure the patient didn't move, then 2 meters is a good parameter." A panel member commented, "I feel the data is good enough at 2 meters… Future studies could be requested at 4 meters."

- **Different efficacy analyses.** The FDA did three different analyses: (1) an intent-to-treat analysis (ITT) with last observation carried forward (LOCF), (2) a per-protocol analysis, with only the observed cases – no information carried forward or extrapolated, and in patients who meet the strict definition, and (3) a worst case analysis, where all patients in the sham group with missing VA measurements are considered responders and all patients in the drug group with missing VA measurements are considered as non-responders. There was a substantial difference in these analyses with Macugen, but the statistician on the panel criticized the use of a worst case analysis, calling it "highly inaccurate" and saying he didn't think the FDA should do that. Dr. Chambers responded, "We thought it would be instructive to give a lower limit to frame the findings."

This panel's reaction to the multi-analyses suggests that Alcon's Retaane (anecortave) may not have a big problem with the FDA over its first Phase III trial, in which about 40% of patients dropped out by one year. The ITT and per-protocol analyses may differ, but the discussion at the Macugen panel suggests that the FDA and the Retaane advisory committee may accept Alcon's excuse for the dropouts and may not make a big deal over the differences in the two analyses of the first

Phase III trial – providing, of course, that the ongoing Phase III head-to-head trial vs. Visudyne is positive and dropouts are not excessive.

➢ **Anti-VEGF safety.** New safety concerns were raised recently about Genentech's Avastin (bevacizumab), and at least one panel member was concerned whether this would affect the safety profile of Macugen. However, this panel member said he would be satisfied with some long-term ERGs in a small patient group.

➢ **Need for long-term data and data on stopping therapy.** The panel's chair said, "The committee comments reflect not so much concerns about the statistical significance of the efficacy but concerns for the future." Dr. Chambers commented, "We won't know for a number of years – a 10- to 15-year study – but if this product otherwise is looking fine, we would label it based on the available data…To the extent we have two-year data, we will list that, and we will amend the data in the future."

➢ **Endophthalmitis.** As of the time of the panel, an Eyetech official said there had been a total of 18 cases of endophthalmitis out of 14,745 injections, for a rate of 0.12%. A change was made in the protocol for the administration of the intravitreal injections. Before the protocol change, the rate of endophthalmitis was 0.18% and since then it has been 0.03%, but he said all of this drop cannot be attributed entirely to the protocol change.

An Eyetech consultant pointed out that:

- Of the endophthalmitis cases, only one patient (0.1% per patient per year) lost >6 lines (30 letters) of vision, and 75% of patients with endophthalmitis continued on drug.
- In ~70% of endophthalmitis cases, there was at least one violation of the injection procedure (e.g., no eyelid speculum used).

The panel members discussed this safety issue. They had some concerns, but not enough to interfere with approval. Basically, they recommended patient and physician education about sterile techniques and signs and symptoms plus follow-up of at least a phone call on Day 3 and an office visit at Week 1.

➢ **Concomitant use of PDT** (QLT's Visudyne). The protocol for the Phase II/III Macugen trials permitted the on-label use of PDT (Visudyne) either prior to or during the study, at the investigator's discretion, for patients with predominantly classic lesions. Thus, PDT use during the studies was not randomized. All PDT given during the study was administered five to 10 days prior to treatment, not at the time of Macugen/sham injection.

The FDA raised questions about how PDT may have confounded interpretation of the efficacy of Macugen, but panel members were not concerned. An Eyetech consultant emphasized that PDT was allowed in the trials, ***per the FDA***, at the investigator's discretion, and no more than one PDT treatment was permitted before entry into the Macugen trials. An Eyetech official reported that eye pain was slightly greater in patients who also got PDT, but he said there was not a clear increase in floaters in patients who got PDT vs. patients who had no PDT. Another Eyetech official pointed out that:

- PDT was available primarily in the U.S. at the start of the Macugen trials.
- Ethical considerations required that PDT be allowed – but only in patients with predominantly classic lesions and only when administered according to the FDA label.
- In 92% of cases, the reading center agreed with how PDT was used during the trial.
- 75% of patients were never exposed to PDT at any time, and there was no evidence of adverse events with co-administration of PDT and Macugen.

FDA Review of Macugen Efficacy by PDT Usage

Measurement	Macugen 0.3 mg	Macugen 1.0 mg	Macugen 3.0 mg	Sham
International Study EOP1003				
Responders who received PDT on study in the Study Eye by ITT at Week 54	1% p=.68	12% p=1.0	13% p=.92	13%
Responders who never received PDT before or during study by Week 54	74%	78%	72.4%	61.4%
Responders who received PDT only before the study – not on study	100%	60%	83.3%	75%
Responders who received PDT only on study – not before the study	56.3%	53%	50%	48%
Responders who received PDT before and during the study	100%	100%	50%	0
North American Study EOP1004				
Responders who received PDT on study in the Study Eye by ITT at Week 54	22% p=.05	25% p=.22	26% p=.26	30%
Responders who never received PDT before or during study by Week 54	64.4%	70.7%	65.7%	58%
Responders who received PDT only before the study – not on study	80%	37.5%	60%	50%
Responders who received PDT only on study – not before the study	72%	57.1%	51.7%	46.2%
Responders who received PDT before and during the study	76.9%	75%	57.1%	41.7%

EYETECH'S PERSPECTIVE

Eyetech officials and experts offered background on AMD – stressing that AMD is an urgent unmet medical need – and on the mechanism of action of VEGF inhibitors. Eyetech's CEO cited a study which found that 85% of retinal specialists are dissatisfied with current AMD treatment options.

The Eyetech Chief Scientific Officer explained that Macugen dosing was based on PK data, and he noted that Macugen targets the VEGF isoform ($VEGF_{165}$), which is operative in disease. He reviewed the clinical safety of Macugen:

- **Thromboembolisms.** He tried to distinguish Macugen from Avastin and other VEGF inhibitors used in chemotherapy, commenting, "One can have a theoretical basis for thromboembolic prevalence that is greater in the cancer and chemotherapy population, which is very different from the AMD population."

- **Eye pain and floaters.** These were greater in study eyes than in fellow eyes, and he said these are probably due to the intravitreal injection rather than Macugen itself. He commented, "A 90 microliter injection displaces the vitreous, and it is not surprising that this will induce floaters. They were never severe…No patients left the trial because of floaters."

- **Cataracts.** Only three patients underwent elective cataract surgery during the trials.

- **Angiography update.** He reported that 97% of Month 18 angiograms and 92% of Month 24 angiograms have been reviewed, and there is no evidence of retinal vascular or choroidal abnormalities that were not consistent with the natural history of the disease.

- **Longer-term safety.** The Independent Data Monitoring Committee has reviewed 100% of patients through Month 18 and 97% of patients through Month 24, and he said it has found no new safety concerns, except perhaps some retinal detachments (six in Year 2). The panel chair also wondered if there should be a precautionary statement about retinal detachments on the label.

A Harvard ophthalmologist who is a consultant for Eyetech explained that intravitreal injections are routinely used for endophthalmitis, retinal detachments, CMV retinitis, and more commonly with DME, retinal vein occlusions, uveitis, and AMD (with PDT). He admitted that there have been severe adverse events with Macugen, but said they are related to the procedure and the rates are comparable to published rates for intravitreal injections. His conclusions were that Macugen has a "very favorable safety profile that may be improved further by education and training…The benefits of Macugen far outweigh the risks."

Other key points about Macugen that were made by Eyetech in the briefing documents included:

- The onset of efficacy was as early as six weeks and appeared to increase up to 54 weeks.
- No baseline characteristic precluded a treatment benefit, including angiographic lesion subtype or size, visual acuity at treatment start, age, gender, prior use of PDT with verteporfin or degree of iris pigmentation.
- Usage of PDT during the studies was low, with increased PDT use in the sham arm. There was no evidence that PDT usage influenced the efficacy of Macugen.
- Macugen doses of 1 mg and 3 mg were effective in combined analyses but did not exhibit additional benefit over that seen at the 0.3 mg dose level.
- Macugen was well tolerated, with few withdrawals due to adverse events.
- No systemic safety issues were apparent.
- The majority of ocular adverse events were judged by investigators to be related to the intravitreal injection procedure.
  - Serious ocular adverse events, including endophthalmitis (0.16% per injection, 1.3% per patient per year), traumatic cataract (0.07% per injection, 0.6% per patient per year), and rhegmatogenous retinal detachment (0.04% per injection, 0.3% per patient per year) were infrequent and also likely related to the injection procedure.
  - Other than iatrogenic traumatic cataracts, there was no evidence that Macugen treatment resulted in cataract progression.
  - There was no evidence of a persistent increase in intraocular pressure associated with Macugen. Transient increases in IOP are expected with intravitreal injections, and such increases were seen with Macugen. The increases were manageable and no patient was discontinued due to increased IOP.

THE FDA PERSPECTIVE

The FDA reviewer reported that in both Macugen trials:

- The total lesion size and the size of the CMV continues to increase for all treatment groups – even patients receiving Macugen – but it does appear that it increases less with 0.3 mg group than with sham.
- Both the 0.3 and the 1 mg dose have about a 15% benefit over sham.
- It appears that patients in the sham group lose vision at a higher rate than in all three other active treatment groups.
- Substantially fewer PDT treatments were given in the 0.3 mg group than in the sham group. She said, "The numbers were too small to determine whether giving PDT before or during the trial has any effect on the results."

Her conclusions were:

- **Efficacy.** She concluded, "We believe 0.3 mg dose does reduce vision loss in AMD patients, but keep in mind that there is only an approximately 15% treatment effect, and there is no improvement in vision."
- **Safety.** She concluded that the endophthalmitis appears to be minimized by new sterile technique, and there is no apparent increased systemic risk.

Another FDA official commented, "The review did not show any big (red) flags."

THE FDA QUESTIONS AND THE ADVISORY COMMITTEE'S VOTES

The FDA withdrew a proposed question that would have had the panel vote on whether the benefits of Macugen in AMD outweigh the risks, but the panel's message was clear nonetheless: this is a product that is safe, at least somewhat effective, and belongs in the armamentarium of retinal specialists. They did, however, recommend patient and physician education to minimize endophthalmitis as well as post-marketing studies to determine the long-term effect, how long patients should receive Macugen, and how best to take patients off of it.

QUESTION 1: Based on the inclusion/exclusion criteria, are there patients excluded from the studies that you believe need to be studied?
NO: By a unanimous vote members agreed that the criteria seem appropriate.

Q2: Visual acuity measurements were conducted using the ETDRS scale placed at 2 meters from the patient. The validity of the ETDRS scale was established based on readings at 4 meters. Are the visual acuity findings sufficiently robust to overcome the potential bias introduced by visual acuity measurements at 2 meters?
YES: By a unanimous vote members said they were satisfied with the robustness of the data.

Q3: Has sufficient data been submitted to evaluate the efficacy and safety profile of Macugen? If not, what additional data are needed?
YES: By a unanimous vote members said that sufficient data has been submitted, though post-marketing surveillance would be useful to determine long-term safety.

Q4: Are additional analyses of the current data needed to understand the efficacy or safety of Macugen for the treatment of age-related macular degeneration?
NO. With one committee member abstaining, all other members voted that no additional analyses are needed.

Q5a: Has the concomitant use of PDT therapy with Macugen been explored sufficiently?
YES: by a unanimous vote.

Q5b: Are there concerns with using this product concomitantly with PDT therapy?
NO: by a unanimous vote.

Q6: Do the route and/or frequency of administration of the drug raise any concerns that are not addressed by the studies?
NO. With two committee members abstaining, the other six members voted that there are concerns but that they have been addressed, though several said they would hope less frequent administration or another delivery method could be developed in the future.

Q7: Endophthalmitis (approximately 2%) was observed in these studies. What is the optimal follow-up needed to minimize the impact of potential endophthalmitis cases?
Panel members agreed that follow-up, patient education, and physician education are all needed, but they left the final timing decisions to the FDA and Eyetech to work out. Most agreed that a phone call at Day 3 and an office visit at Week 1 should be done.

Q8: Are there adverse experiences that are of particular concern for this product?
NO: by a unanimous vote.

Q9: Vascular Endothelial Growth Factor (VEGF) has been shown to be an important component in the development of collateral vessels in ischemic heart disease. Inhibition of VEGF in the systemic circulation could present a theoretical increased risk of symptomatic cardiovascular disease in the target population of elderly patients with AMD.

- Has the adverse event profile of the two randomized Phase III trials raised any concern over the possible systemic effects of this therapy? **NO: by a unanimous vote.**
- Is there additional monitoring that should be in place for patients on Macugen therapy? **YES: just long-term safety monitoring, not additional studies.**

After the committee meeting concluded, Dr. Chambers met with reporters and answered questions about the panel meeting.

- **On the overall panel tone.** He doesn't consider the panel votes as recommendations on approval, and he would not characterize his impression of the panel votes except to say: "We asked a number of difficult questions, and the panel felt we should be able to make a decision...that the analysis is sufficient. There is additional information they would like

studied but not necessarily before approval. The agency will factor all of this into its decision…The panel did not bring up any particular new points that are show stoppers."

- **On endophthalmitis.** He said: "There is clear concern about that, how best to minimize it, and how best to follow-up on it…The agency is very interested in those comments."

- **On the panel's message on the overall safety of Macugen.** He said the panel indicated: "There are safety concerns, but they have been studied, and we should use the information we have and factor them into our decision."

- **On whether two-year data will be required.** He said, "With Visudyne, we made a conscious decision that one-year data was an important endpoint for AMD patients. Even if the product (Visudyne) were to lose efficacy at two years, that would become a labeling issue. And we did that, in fact, with high myopia. We said Visudyne works for high myopia but the effect is no longer there at two years."

- **On the lack of discussion of the data pooling or efficacy across lesion size/type.** He said, "We provided an opportunity to bring those issues up – and they didn't."

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