Comparison of AMD Treatment Trials (CATT): Lucentis - Avastin Trial

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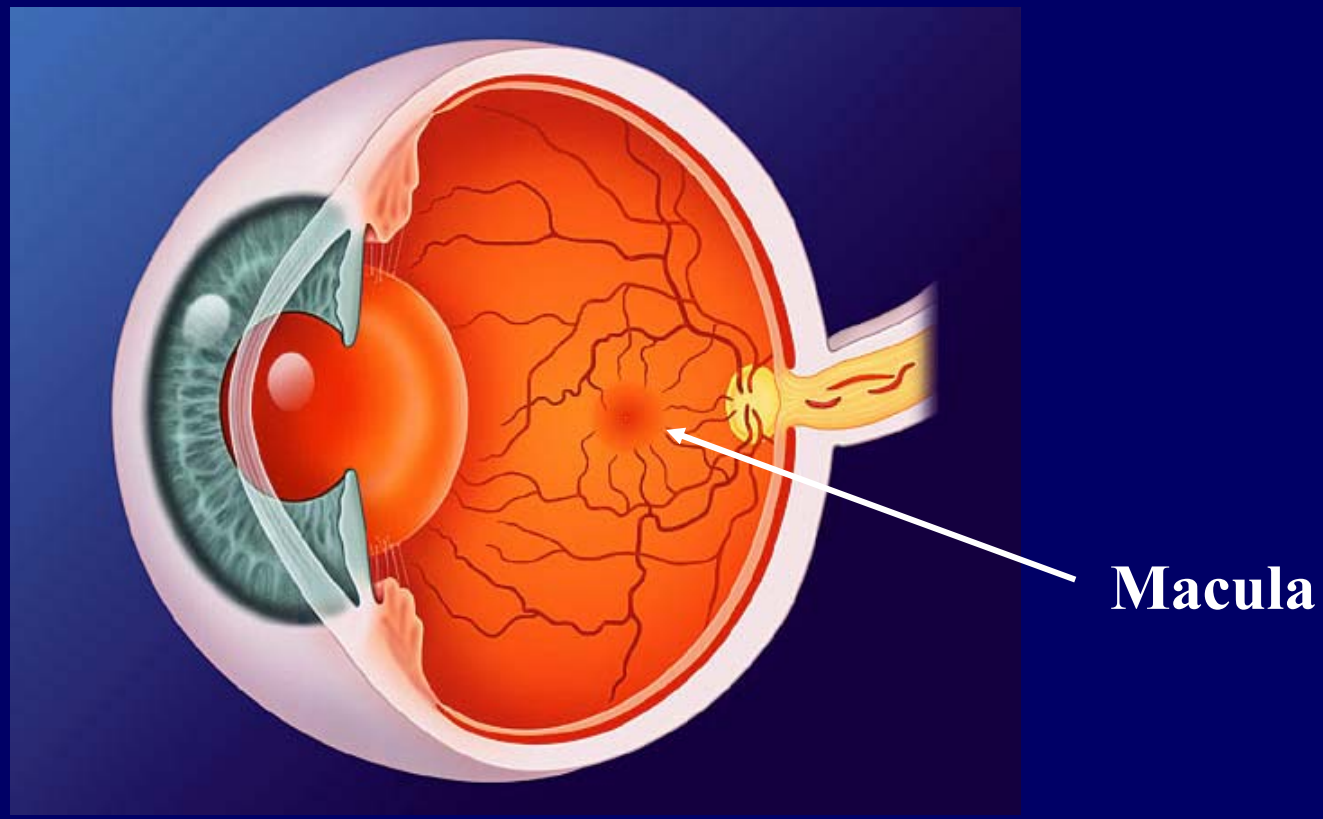
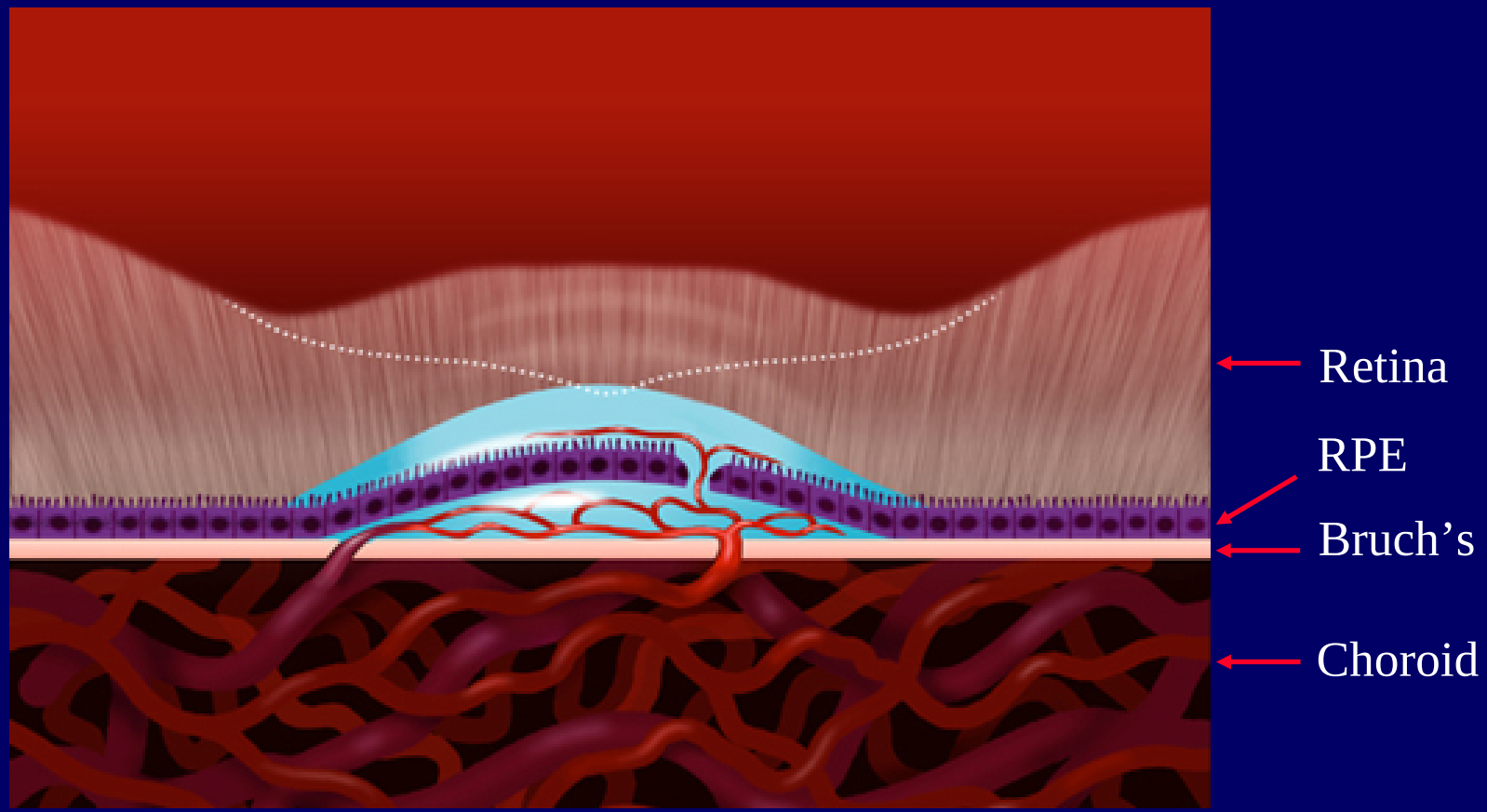
Age-Related Macular Degeneration

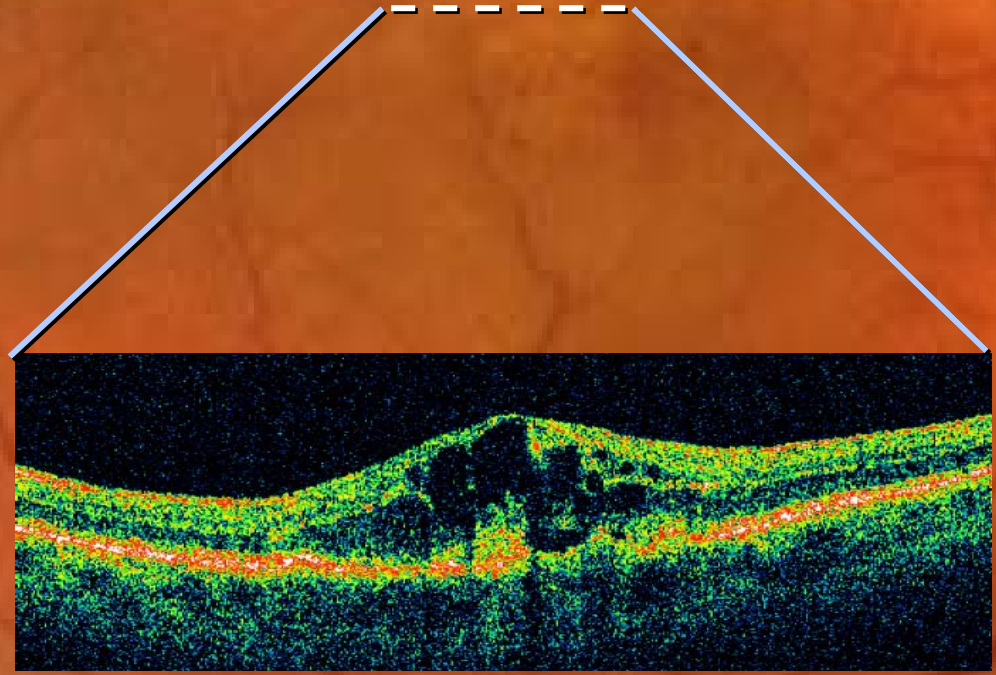
- Leading cause of vision loss in patients > 65 years
- 9 Million in the US at high risk for progression to advanced AMD



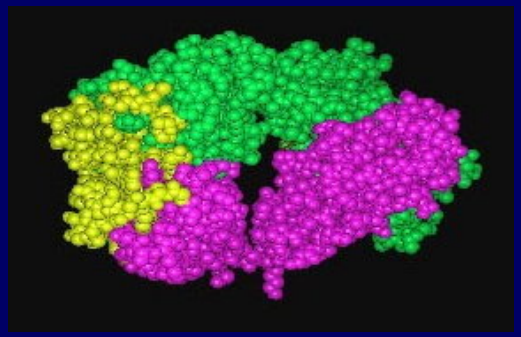
Neovascular (Wet) AMD



Neovascular (Wet) AMD

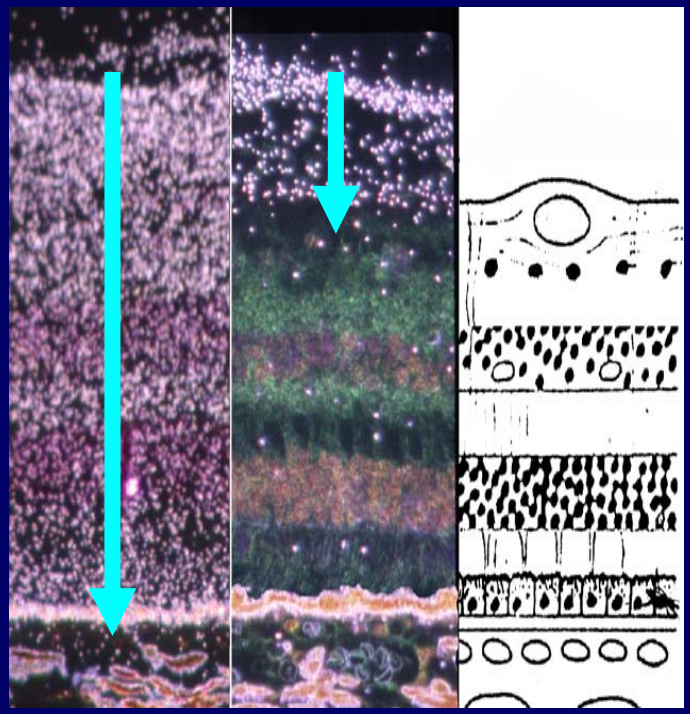


Lucentis

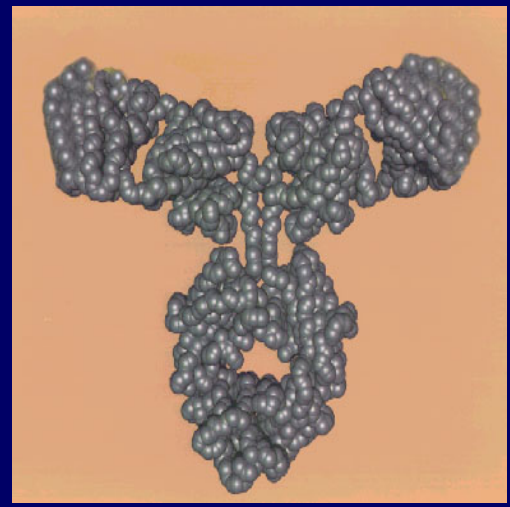


Fab
MW 48,000

- recombinantly produced
- humanized
- Fab fragment
- Mouse Monoclonal Ab vs VEGF
- V2 – Version 2 Affinity Matured



Fab **IgG**

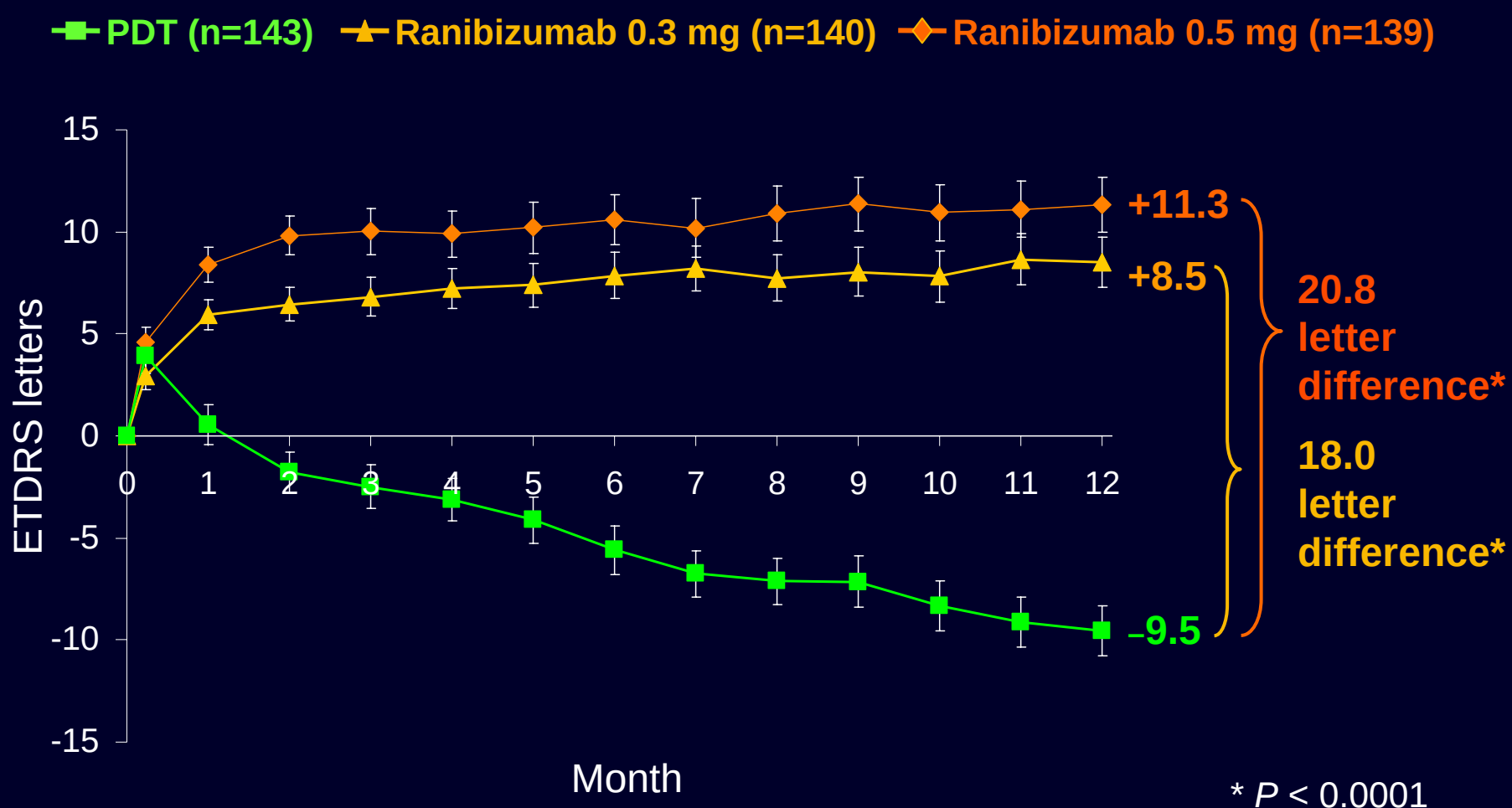


IgG

GNE Study
98-223-1757

rhuFabV2 penetrates through all retinal layers while IgG only penetrates superficially.

Secondary Endpoint:
Mean Change in Visual Acuity Over Time



Note: Vertical bars are ± one standard error of the mean.

Treatment Efficacy at One Year

	≤ 3 Line Loss	≥ 3 lines gained	≥ 20/40	Mean Change VA (letters)
Laser	50%	1%	---	
PDT	67%	6%	5%	- 10
Macugen	70%	6%	---	- 7
Lucentis				
MARINA	95%	34%	40%	+ 7
ANCHOR	95%	40%	39%	+ 11

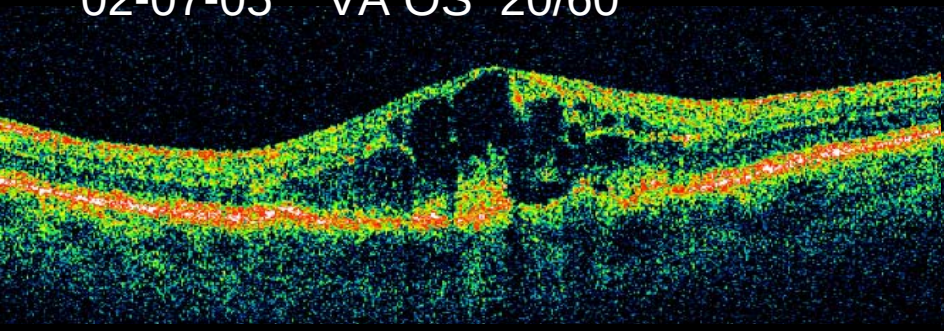
Avastin

- Bevacizumab is a monoclonal antibody against VEGF that is similar to the one from which Lucentis was derived.
- Approved for treatment of colorectal CA in 2004; available for off-label use
- Single case of intravitreal Avastin for neovascular AMD presented at ASRS meeting in July 2005
- Estimated that over 50,000 eyes subsequently treated with no prospective clinical trial data to support its use

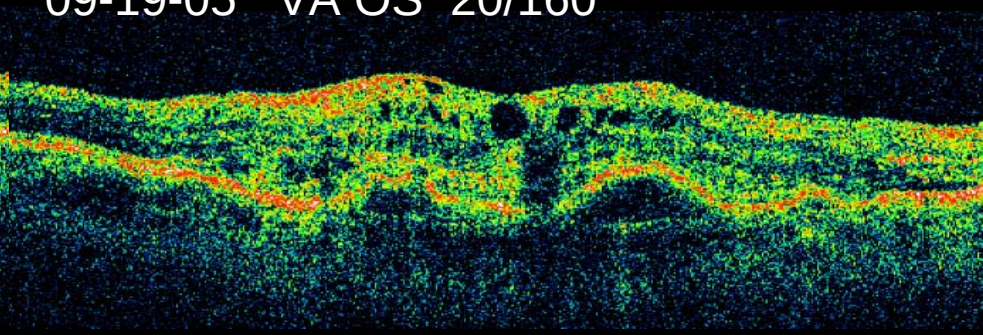
Treatment with Avastin

74 y/o WF, Disciform OD, CNVM OS

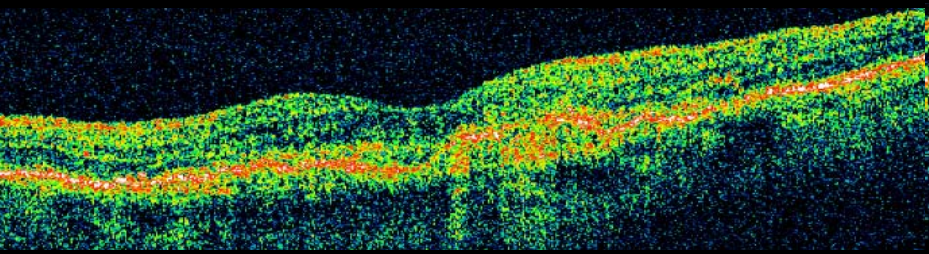
02-07-05 VA OS 20/60



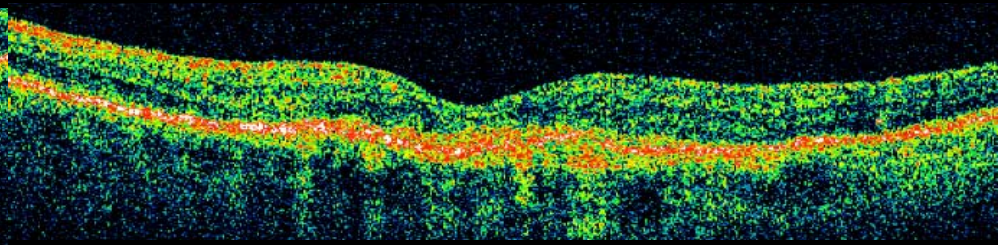
09-19-05 VA OS 20/160



09-26-05 VA OS 20/80



11-17-05 VA OS 20/60



CATT Study Officers

- Daniel F. Martin MD – Chair (Emory)
- Stuart L. Fine MD - Vice Chair (Penn)
- Maureen Maguire PhD – Coordinating Center (Penn)
- Glenn J. Jaffe MD – OCT Reading Center (Duke)
- Juan Grunwald MD - Photo Reading Center (Penn)

CATT Design (Fall, 2005)

- Goal was to determine efficacy and safety of Avastin relative to Lucentis
- Lucentis only studied with fixed (every 4 week) dosing; Avastin had only been given on an as needed basis
- Anecdotal experience with as needed dosing of Avastin (and later Lucentis) was extremely favorable
- Need to understand whether long term visual outcomes were compromised with less frequent dosing; only be determined in a RCT

Lucentis-Avastin Trial (October 2006)

1200 patients with newly diagnosed neovascular AMD randomly assigned to:

- **Lucentis fixed**
- **Avastin fixed**
- **Lucentis as needed**
- **Avastin as needed**

To be conducted at 47 sites in the US

Lucentis-Avastin Trial

- Primary Outcome Measure
  - mean change in visual acuity
- Secondary Outcome Measures
  - Number of treatments
  - 3-line change in VA (15 letters on ETDRS chart)
  - Change in subretinal and intraretinal fluid on OCT
  - Change in lesion size on fluorescein angiography
  - Cost of treatment
- Genetics, pharmacokinetics modules; combination therapies reserved for subsequent trial
- Follow up for 2 years with plans to report one-year data in 2009

Funding

- Total cost of study = $50 Million
- NEI granted $16.2 Million over a 4 year period to fund the infrastructure of the trial (coordinating center, photo and OCT reading centers, clinic coordinators, etc) effective Oct 1, 2006
- Remaining $34 Million is patient care cost
- Medicare and supplemental policies already responsible for standard patient care costs
- Would Lucentis and Avastin be covered?

Lucentis and Avastin

- Cost of Avastin about 1 million dollars (drug cost, central compounding and distribution) – paid by grant
- Cost of Lucentis in this trial is $22-25 million dollars.
- Genentech has stated publicly many times (twice in WSJ) that they would not support the trial.
- Given that percent of projects funded by NIH is at an all time low, not reasonable to expect NIH to cover cost of Lucentis
- CMS already responsible for care in majority of patients

CMS

- First meeting with CMS in July 2006
- Could not legally pay even the 80% of Lucentis in a clinical trial without changes to the Medicare Clinical Trial Policy
- Difficult to understand when Lucentis was already FDA approved and existing policy stated that routine care in a clinical trial was covered with routine care defined as "Items or services that are typically provided absent a clinical trial (e.g., conventional care)"
- Lucentis deemed as investigational
- This trial became an important stimulus for the Revised Medicare Clinical Trial policy

Masking

- No payment mechanism in place that would allow for central masking of identity of the drug
- Need an initial cash outlay of $25 million to centrally purchase drug. Drugs would be masked, distributed to clinics, administered locally, and billed in such a way that central purchaser could recover cost.
- If CMS could pay 80% of drug cost, patient responsible for 20% co-pay. Different amounts of co-pay ($400 vs $10) unmasks patient and encourages differential drop-out.
- Medicare patients receive a MSN that identifies the drug billed, thus unmasking the patient
- 85% Medicare beneficiaries have a supplemental policy that also identifies the drug and amount paid thus unmasking patient

Solution

Demonstration Project

- CMS payment method mimics a research grant award
- CMS provides “up front” payment to the study for purchase and distribution of study drugs
- Central record keeping of drugs distributed in the trial; patients receive no bills for drug injections
- CATT would demonstrate the benefits of giving the money to a trial organization (with appropriate accounting safeguards in place) to support head-to-head comparisons of covered drugs. The masking issue and the co-pay issue are common to many trials.

AMD Treatment Costs

- **Project does not expand coverage**
- **Treatment of 1200 patients participating in Lucentis – Avastin Trial generates substantial savings for CMS**
- **Drug cost to CMS (80% of total) if 1200 patients receive:**

Lucentis similar to Genentech trials	**$50 Million**
Treatments as in CATT	**$25 Million**

- **Savings to CMS** **$25 Million**

CMS

- Project would in essence pay the co-pays and it would take Congressional authority to do so.
- Demonstration project not appropriate mechanism for this circumstance
- Pursue legislative efforts to obtain funds.

CMS

- November 2006 – determined that a demonstration project may be an appropriate mechanism
- December 2006 – March 2007, many different plans were developed.
- Obvious during the process that there was no precedent for doing this.

CATT Demonstration Project

- Lucentis and Avastin billed by clinics using a G-code identified on the MSN and by the supplemental policies as the Lucentis-Avastin study drug.
- Price was average cost of the two drugs plus a small margin that had been built in on the basis of the assumed inbalance in Lucentis and Avastin usage in as needed dosing arms.
- The NEI would have paid the balance of all co-pays after Medicare and the supplemental policies had paid.
- Patients would have had no out of pocket expense and remained fully masked.
- Issue of initial cash outlay and financial liability unresolved

CATT Demonstration Project

- **Full support by CMS**
- **Approved by OGC/CMS**
- **Signed by CMS Administrator in May 2007**
- **Sent to HHS and OMB for approval. Discussions with each of these offices suggested strong support**
- **Three months later informed that OGC/HHS had deemed the project as unapprovable**
- **Only justification provided was that "it was so obvious that the demonstration project would improve the quality of the clinical trial and Medicare beneficiaries participation in it that we did not need to do the project to prove it."**

Lucentis-Avastin Trial

- CATT is fully funded and ready to begin
- Investigator meeting Sept 24-25 with 47 clinical sites in attendance
- Revised Medicare Clinical Trial Policy supports Lucentis use in the trial; Avastin covered by NEI funds. NEI will pay co-pays not covered by supplemental policies.
- Masking at local level with masked visual acuity examiners and masking of the treating physician. Patients will be unmasked.
- Continue to work with CMS on an alternative plan that would allow full masking
- The goal is to have first patient enrolled by end of 2007

Summary

- CMS has worked hard to resolve these issues
- Limited by an inflexible and inefficient system.
- No culture of communication with outside investigative groups. Decisions by OGC unilateral with no opportunity to discuss.
- Program should be established where CMS can provide up front funding for drugs in a clinical trial if cost-neutral to CMS and CMS deems it is in the public's best interest to do so.

Summary

- **The CATT Lucentis – Avastin trial has been delayed for more than a year as a result of these issues.**
- **Study will define best treatment strategies to maximize visual outcome with lowest treatment burden and cost for the most common cause of legal blindness in the US.**
- **If Avastin is equivalent to Lucentis or if the treatment burden is reduced, cost saving estimated by CMS (on basis of previous AMD claims) is $1 to 3 Billion each year.**