Macugen (pegaptanib sodium)

Addressing unmet AMD treatment needs through:

- Disease-specific mechanism of action
- Targeted delivery
- Excellent safety profile and compliance

Macugen Patient Benefits

- Broadest indication of any wet-AMD modality
- No drug-related SAEs
- Tolerant of adjunctive treatment
- Slows severe vision loss
- Promotes improvement in visual acuity

The Angiogenic Pathophysiology of Exudative (Wet) Age-Related Macular Degeneration (AMD)

Age-Related Macular Degeneration: Leading Cause of Severe Vision Loss in the Elderly[1]

Typical classification[1,2]

- Nonexudative (dry)
  - Accumulation of drusen in the retina /geographic atrophy
- Exudative (wet)
  - Choroidal neovascularization

AMD risk factors[2]

- Age (over 50 years)
- Smoking
- Caucasian race
- Family history

References: 1. Elman MJ, Fine SL. Exudative age-related macular degeneration. In: Ryan SJ, ed. *Retina.* Vol 2. 2nd ed. St Louis: Mosby Publishers; 1994:1103-1141. **2.** Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol*. 2003;48:257-293.

Exudative (Wet) AMD

Nonexudative AMD

- Progresses over many years[1]
- Prevalence = 4.7 million[2]; annual incidence = 4.0%[3] (1999 US Medicare population)
- ~2% of patients with dry or unspecified AMD progress to wet AMD in a given year[3] (1999 US Medicare population)

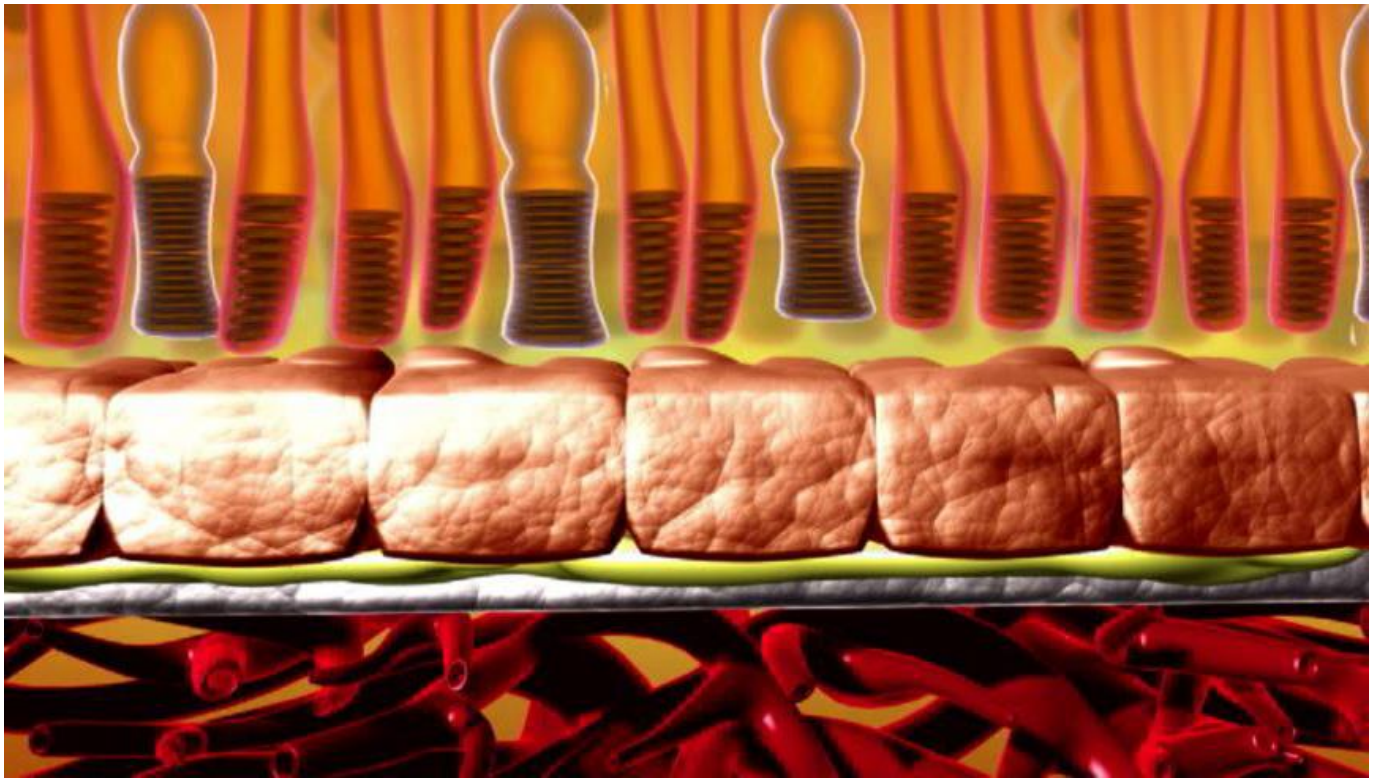
Exudative AMD

- Progresses over 1 to 2 years[1]
- Prevalence=1.8 million[2]; annual incidence=1.1%[3] (1999 US Medicare population)
- Estimated incidence=200,000 new cases per year[4]
- Accounts for 10% of all AMD and 90% of all severe vision loss[1]

References: 1. National Eye Institute. Facts about age-related macular degeneration. Available at: http://www.nei.nih.gov/health/maculardegen/armd_facts.htm. Accessed July 22, 2003. **2.** Lee PP, Feldman ZA, Ostermann J, Brown DS, Sloan FA. Longitudinal prevalence of major eye diseases. *Arch Ophthalmol.* 2003;121:1303-1320. **3.** Sloan FA, Brown DS, Carlisle ES, Ostermann J, Lee PP. Estimates of incidence rates with longitudinal claims data. *Arch Ophthalmol.* 2003;121:1426-1468. 4**.** Data on file. Pfizer Inc. New York, NY.

Clinical Hallmark of Nonexudative (Dry) AMD[1]

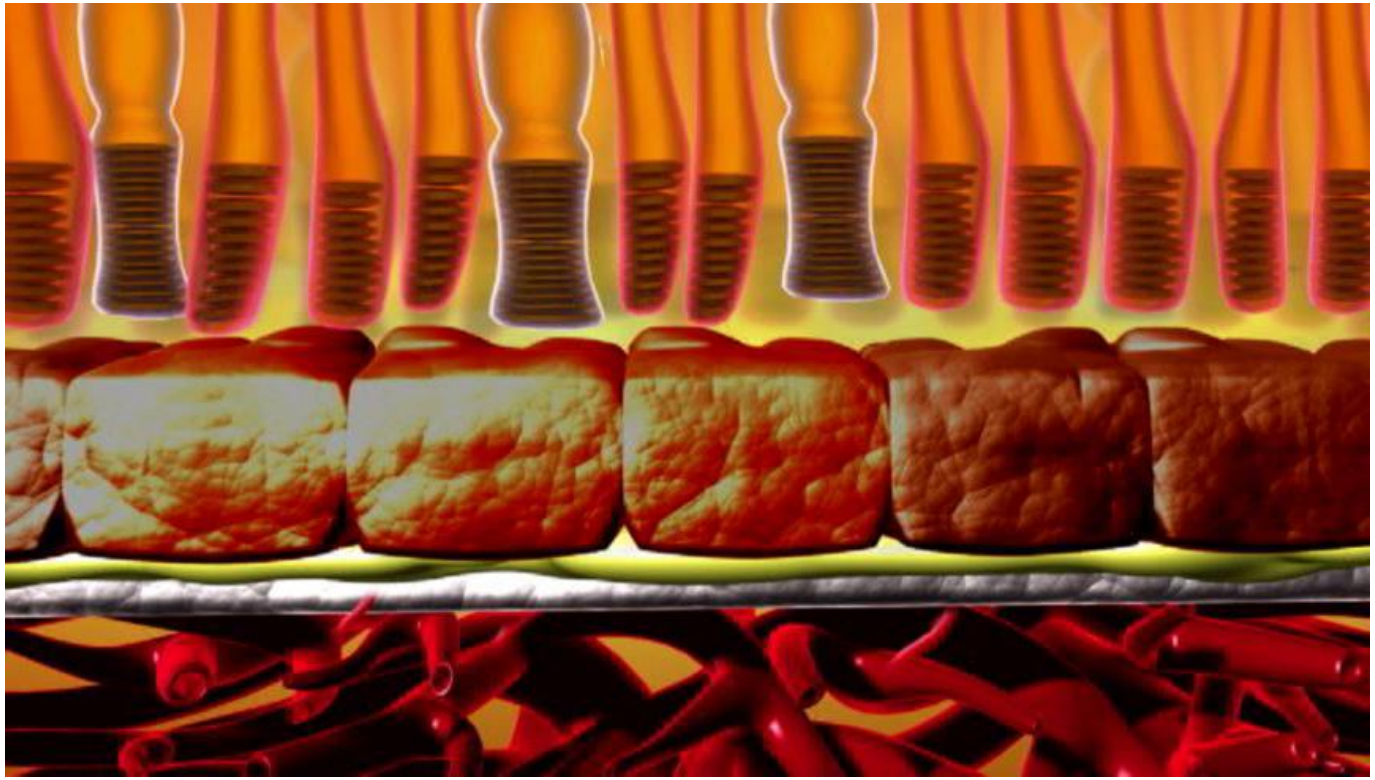
- Localized deposits of drusen lying between the retinal pigment epithelium (RPE) and Bruch's membrane [1]



Reference: 1. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol*. 2003;48:257-293.

Areas of Confluent Drusen and Focal Hyperpigmentation of RPE Cells

- Independent risk factors for development of choroidal neovascularization (CNV) and wet AMD[1]

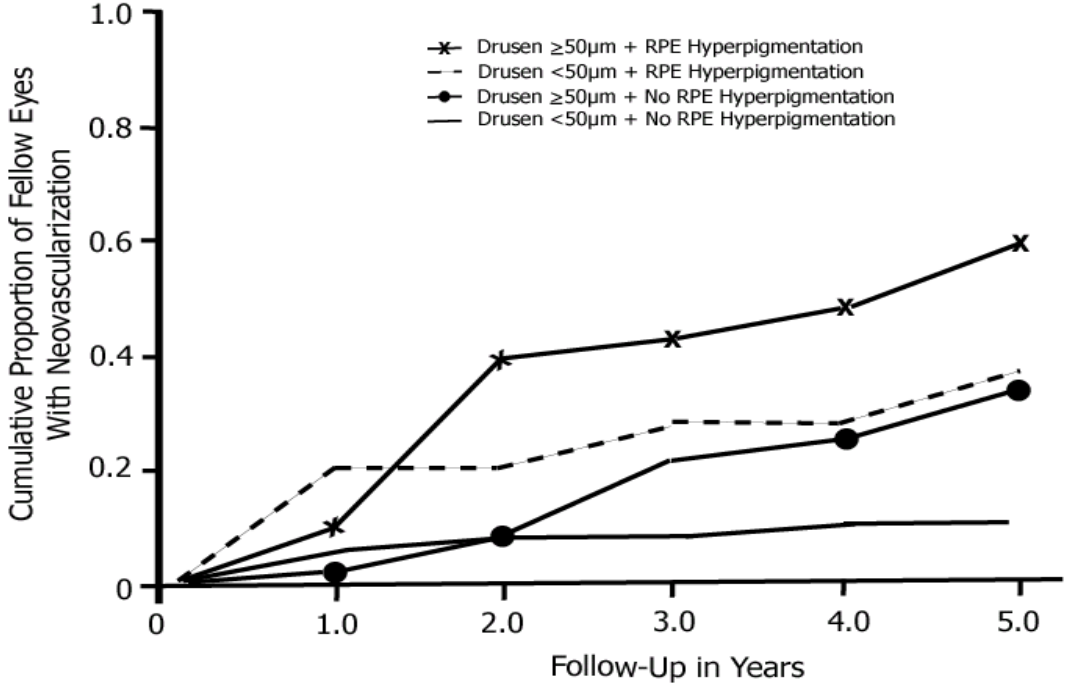


Reference: 1. Bressler SB, Maguire MG, Bressler NM, Fine SL. Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. The Macular Photocoagulation Study Group. *Arch Ophthalmol.* 1990;108:1442-1447.

High Risk Dry AMD Eyes

Progression to CNV over 5-years follow-up:

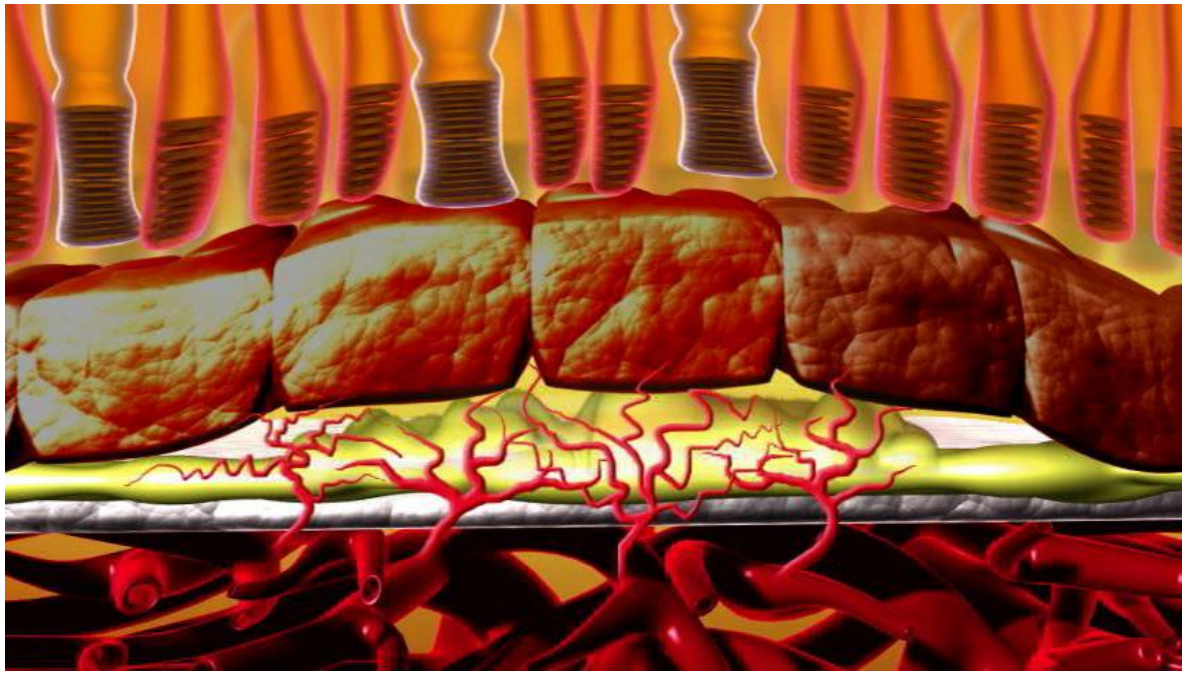
- 10% of eyes without RPE hyperpigmentation and large drusen
- 58% of eyes with both RPE hyperpigmentation and large drusen



Reprinted with permission from Bressler SB, Maguire MG, Bressler NM, Fine SL. Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. The Macular Photocoagulation Study Group. *Arch Ophthalmol.* 1990;108:1445.

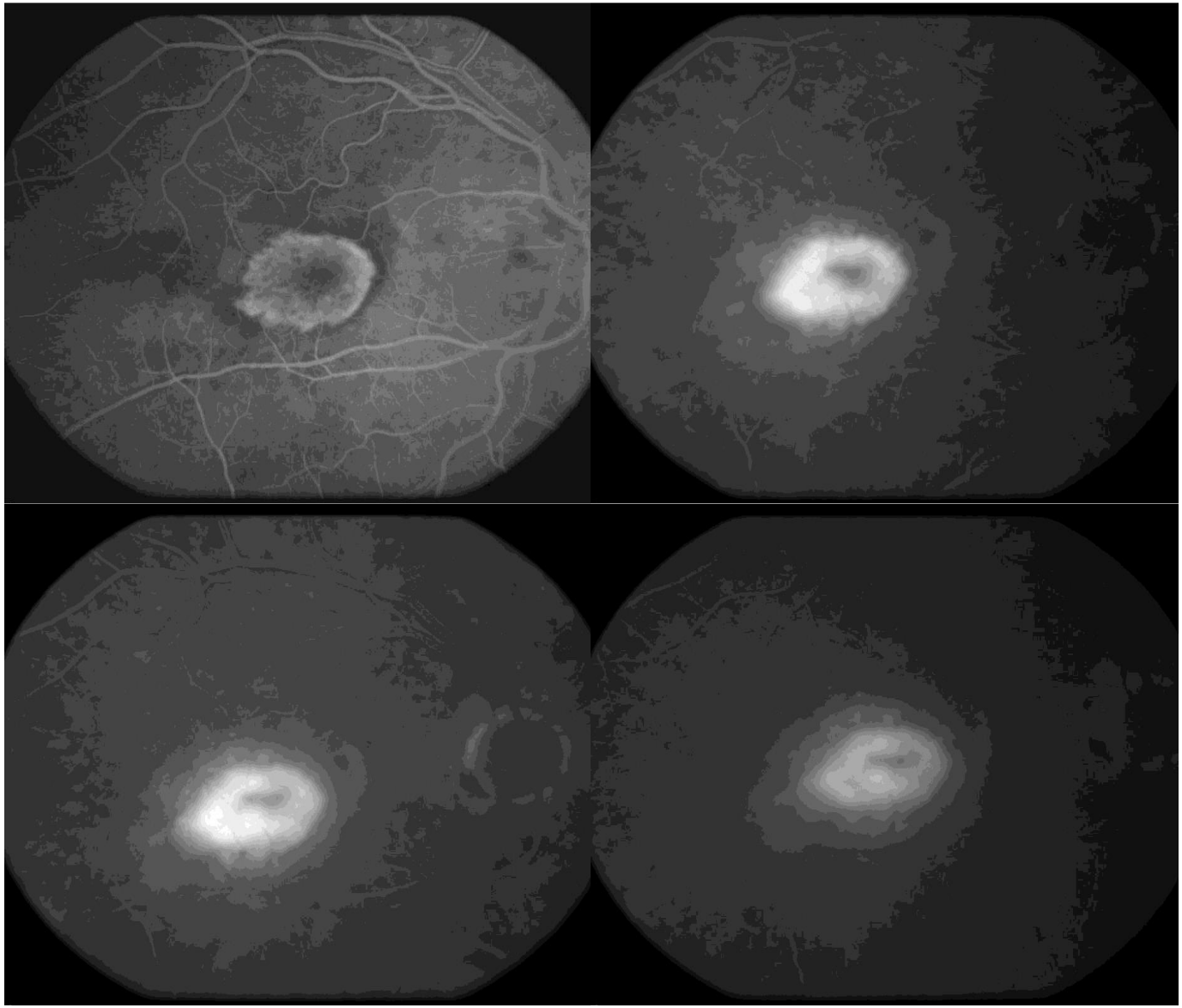
CNV:
The Principal Cause of Vision Loss in AMD

- Small, highly permeable choroidal vessels contribute to RPE detachment; new vessels grow, break through Bruch's membrane, and begin to leak and hemorrhage[1]



Reference: 1. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol.* 2003;48:257-293.

Predominantly Classic CNV



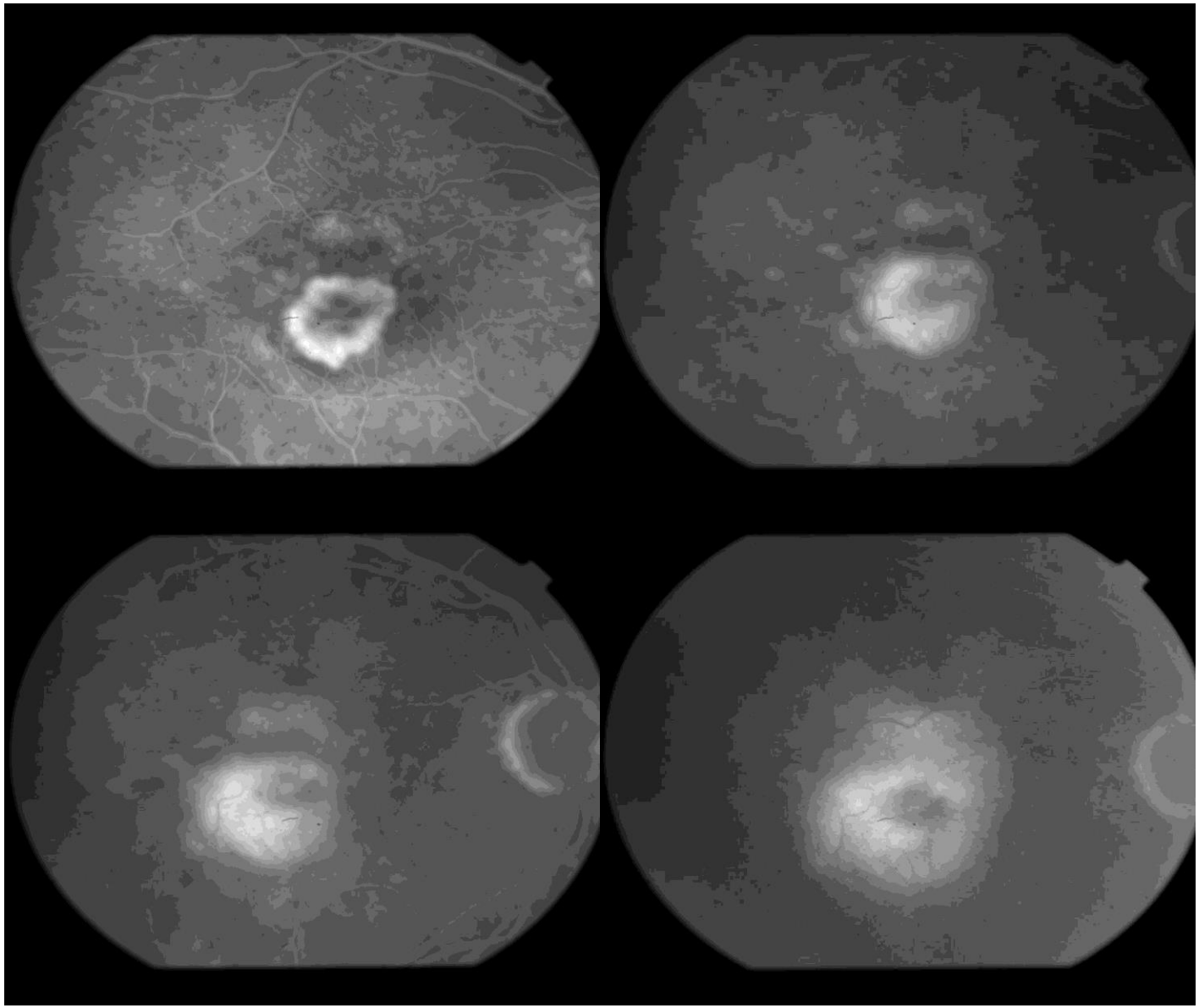
100% in this case

Borders of CNV well-defined early

Dye leakage quickly obscures borders of CNV

Leakage persists in late frames

Minimally Classic CNV

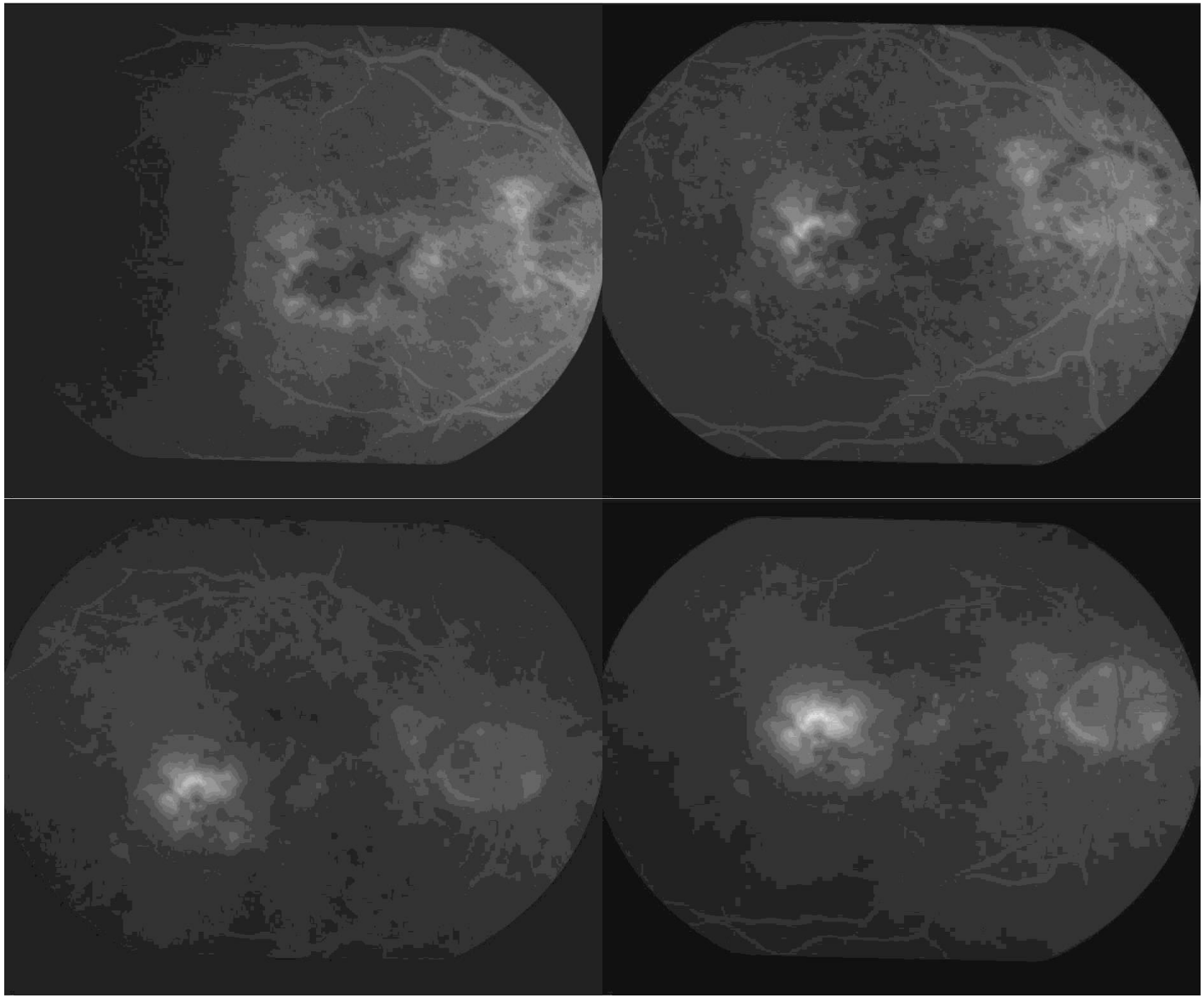


<50% lesion with well-defined CNV

Dye leakage obscures borders of CNV

Leakage persists in late frames

Occult CNV



Borders typically poorly defined

Leakage of dye less intense and may occur in late phase only

Current Therapeutic Options

Laser therapy:

– only appropriate for juxtafoveal and extrafoveal lesions[1]

PDT

– only approved for predominantly classic CNV[2]
– associated with severe vision loss in up to 5% of patients[2]
– 90% recurrence rate for treated eyes

High unmet medical need: 75% of wet AMD patients have no treatment options

References: 1. Ciulla TA, Danis RP, Harris A. Age-related macular degeneration:a review of experimental treatments. *Surv Ophthalmol*. 1998;43:134-146. **2.** Visudyne® (verteporfin) [package insert]. Duluth, GA: Novartis Ophthalmics; 2002.

Meeting the Need for New Therapies[1]

Treatments targeted to underlying angiogenic processes may halt or reverse CNV[1]

- Steroids administered by intravitreal injection or implant, or by sub-tenon injection[1]
- Vascular Endothelial Growth Factor (VEGF) inhibitors block VEGF interaction with receptors on blood vessels[1]

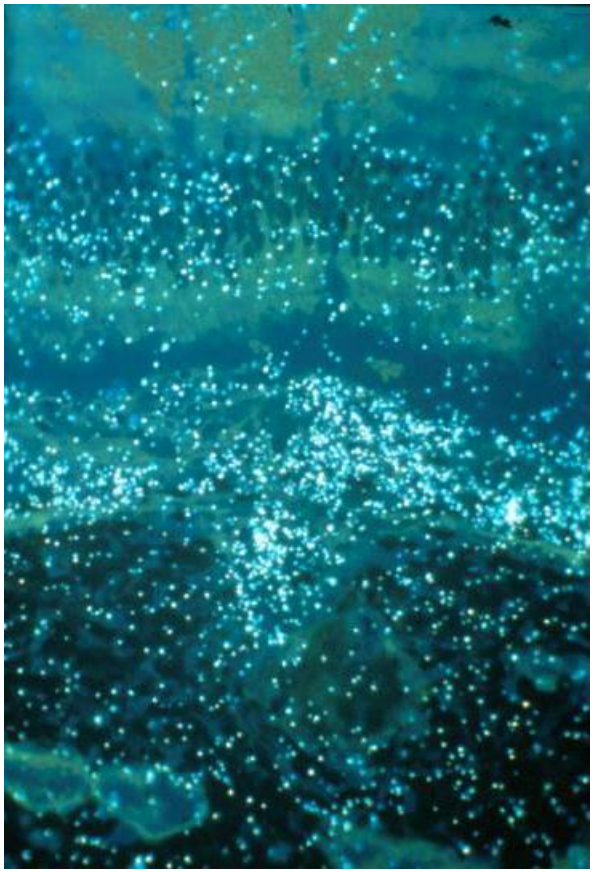
Reference: 1. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol*. 2003;48:257-293.

Vascular Endothelial Growth Factor (VEGF): The "Master Switch" in Angiogenesis[1]

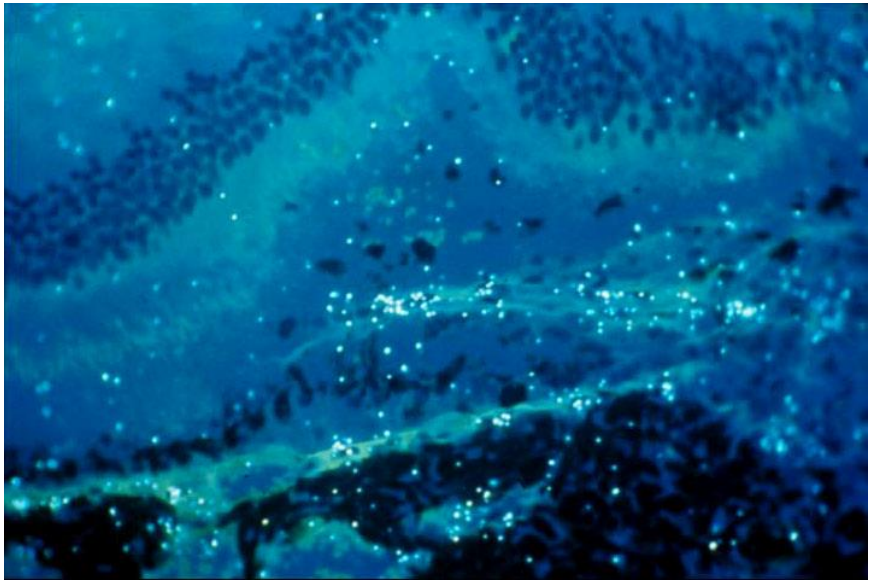
- Highly selective for endothelial cells[1]
- Can diffuse to its target because it is secreted[1]
- Triggers angiogenesis as well as vascular permeability[1]

References: 1. Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. *Nat Med.* 2003;9:669-676.

High VEGF Levels in CNV



VEGF Receptors Expressed Around CNV



VEGF Receptors Expressed on CNV

Reprinted with permission from Joan Miller and Tony Adamis.

Role of “Pathogenic” VEGF

- Induces endothelial cell migration/proliferation[1,2]
- Attracts and activates inflammatory cells[3]
- Promotes new vessel survival[4]
- Triggers vessel permeability[5]

References: 1. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science.* 1989;246:1036-1039. **2.** Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. *Nat Med.* 2003;9:669-676. **3.** Ishida S, Usui T, Yamashiro K, et al. $VEGF_{164}$-mediated inflammation is required for pathological, but not physiological, ischemia-induced retinal neovascularization. *J Exp Med.* 2003;198:483-489. **4.** Alon T, Hemo I, Itin A, Pe’er J, Stone J, Keshet E. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. *Nat Med.* 1995;10:1024-1028. **5.** Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science.* 1983;219:983-985.

VEGF Injections in Primates

- Induce neovascularization in iris[1] and retina[2]
- Promote retinal vascular permeability[3]

1. Tolentino MJ, Miller JW, Gragoudas ES, et al. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. *Arch Ophthalmol* 1996;114:966.

2. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. *Ophthalmology.* 1996;103:1820-1828.

3. Tolentino MJ, McLoed DS, Taomoto M, Otsuji T Adamis AP, Lutty GA. Pathologic features of vascular endothelial growth factor in the nonhuman primate. *Am J Ophthalmol.* 2002;133:373-385.

Blocking All VEGF Isoforms Inhibits Physiological and Pathological Processes[1]

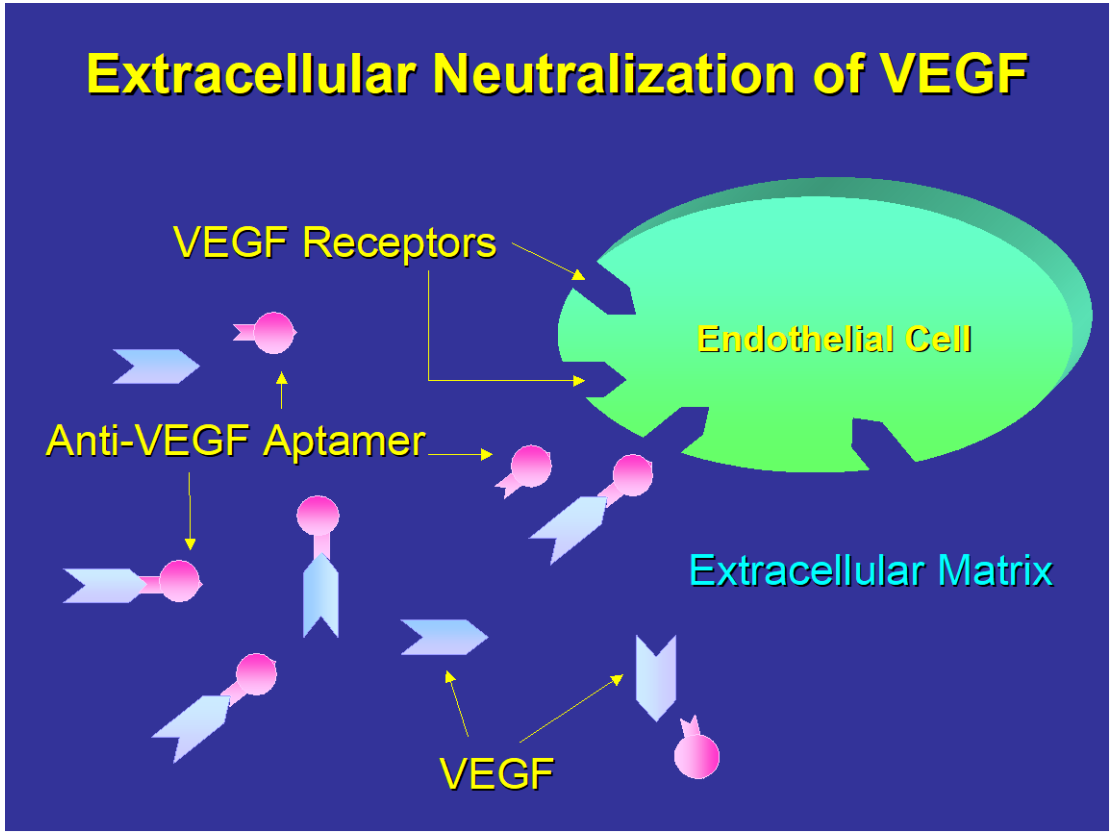
- Physiological: New vessels extend from the optic disc to peripheral avascular retina, under the guidance of VEGF-expressing astrocytes

- Pathological: New vessels invade the vitreous, leading to fibrovascular proliferation, resulting in vitreous hemorrhage and retinal detachment

Reference: 1. Ishida S, Usui T, Yamashiro K, et al. $VEGF_{164}$-mediated inflammation is required for pathological, but not physiological, ischemia-induced retinal neovascularization. *J Exp Med.* 2003;198:483-489.

Macugen™ Selectively Blocks Pathologic VEGF

- Aptamer (oligonucleotide)
- Neutralizes extracellular VEGF
- High affinity for pathologic $VEGF_{165}$ isoform
- Targets underlying cause of CNV



Mechanism Summary

- CNV is the principal cause of vision loss in wet AMD[1]
- Angiogenic growth factor proteins (VEGF) serve as the potential "master switch" for CNV[1,2]
- VEGF exists as several protein isoforms, which have distinct roles in the creation and function of normal and pathological vessels[3,4]
- Effective therapies should target the underlying angiogenic processes of CNV -- specifically, only isoforms responsible for disease

Reference: 1. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol.* 2003;48:257-293. **2.** Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. *Nat Med.* 2003;9:669-676. **3.** Robinson CJ, Stringer SE. The splice variants of vascular endothelial growth factor (VEGF) and their receptors. *J Cell Sci.* 2001;114:853-865. **4.** Ishida S, Usui T, Yamashiro K, et al. $VEGF_{164}$-mediated inflammation is required for pathological, but not physiological, ischemia-induced retinal neovascularization. *J Exp Med.* 2003;198:483-489.

VISION

VEGF Inhibition Study In Ocular Neovascularization

- Pegaptanib sodium (Macugen)
- Largest wet AMD clinical trials ever performed
- 117 leading centers
- Rigorous design; Broadest entry criteria
- Rapid recruitment
- One-year endpoint
- Fastest dissemination of study results: < 1 month
  - Top-line efficacy/safety analysis finalized: 10/16/03
  - Dissemination of analysis to investigators: 11/14/03

Macugen (pegaptanib sodium for injection)

- Conjugate of 28-mer oligonucleotide and 20 kD monomethyl polyethylene glycol (PEG)

(show structure here)

Macugen Binds VEGF165

Attacks a Root Cause of CNV leading to AMD

Macugen

- Selectively binds to pathologic VEGF 165 isoform, while sparing normal vasculature
- Anti-angiogenesis and anti-permeability effects through single VEGF-binding mechanism

VISION Trial Design

Largest Wet AMD Study Ever Performed

- **Two Phase IIIs - 1,186 patients at 117 centers worldwide**

- **All subtypes: Wilmer pre-read**
- **Vision at entry: 20/40 to 20/320**
- **Lesion ≤ 12 total disc areas**
- **Both early and advanced lesions**

Unique - Broad Entry Criteria

"All Comers"

- **Randomized to** **0.3 mg** **1 mg** **3 mg** **Sham**

Intravitreal injection every 6 weeks

- **PDT permitted for predominantly classic lesions (before and during study)**

- **Well-balanced subject baseline characteristics**

VISION Patient Characteristics

Baseline Characteristics	Macugen (n = 890)	Sham (n = 296)
Male / Female (%)	42 / 58	40 / 60
Mean Age (years)	76.0	75.7
Mean Visual Acuity Score (letters)	51.5	52.7
Fellow Eye Mean Visual Acuity Score (letters)	55.6	57.1
Subtype (%)		
Predominantly Classic	27	27
Minimally Classic	35	35
Occult	38	38

Met Primary Endpoint at 54 Weeks

70% of Patients Lost Less than 3 Lines of Vision

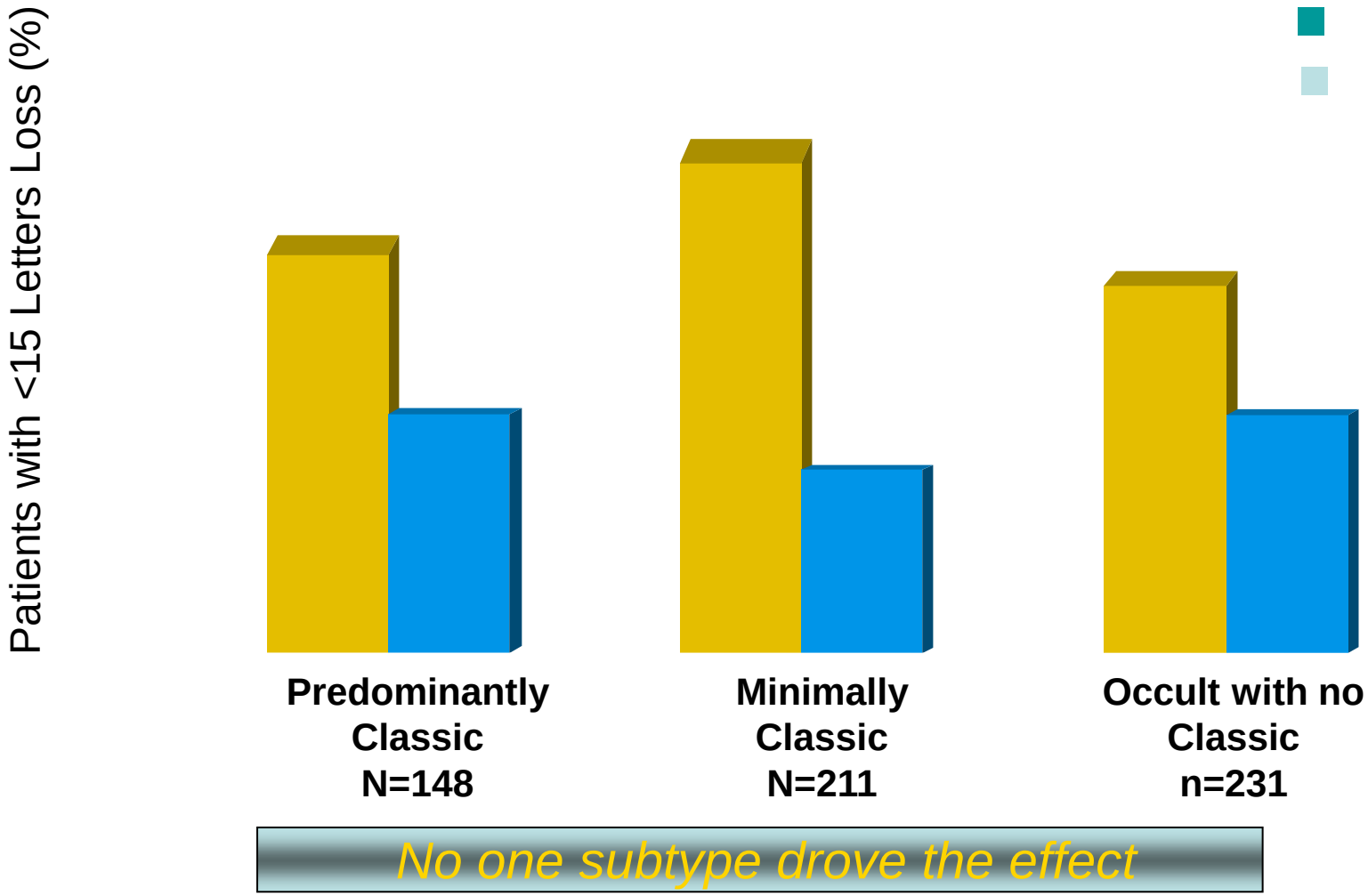
	Combined Analysis (n = 1186)	
0.3 mg	**70%**	**0.0001**
1 mg	71%	0.0003
3 mg	65%	0.0310
Control	**55%**	**–**

27% relative increase in responders for 0.3 mg dose

0.3 mg dose statistically significant in each individual trial:
p=0.003 and p=0.011

Efficacy Among All Subtypes

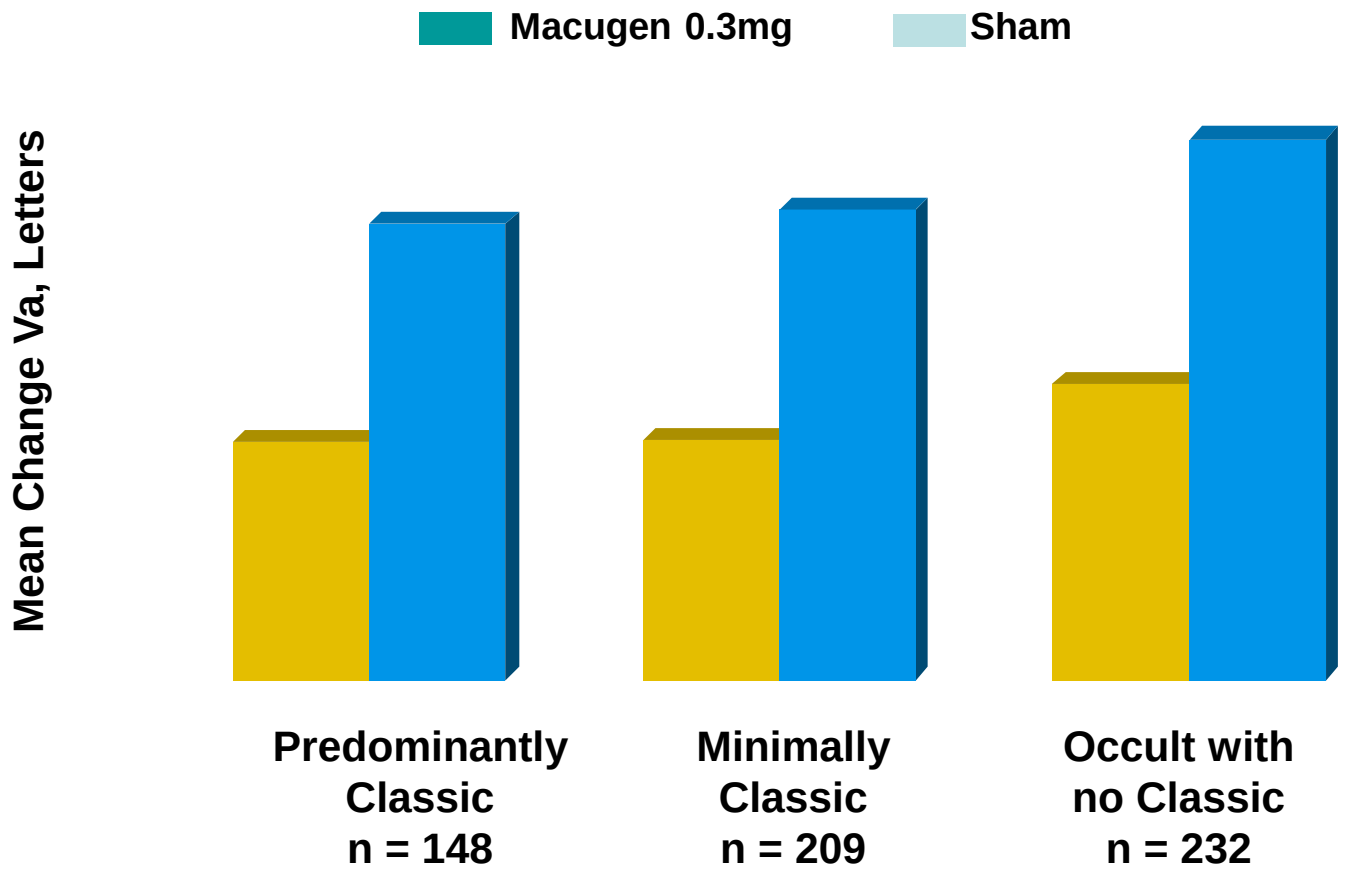
Proportion of patients Losing less than 15 letters



No one subtype drove the effect

Efficacy Among All Subtypes

Mean change in V.A. (Letters) at 54 weeks



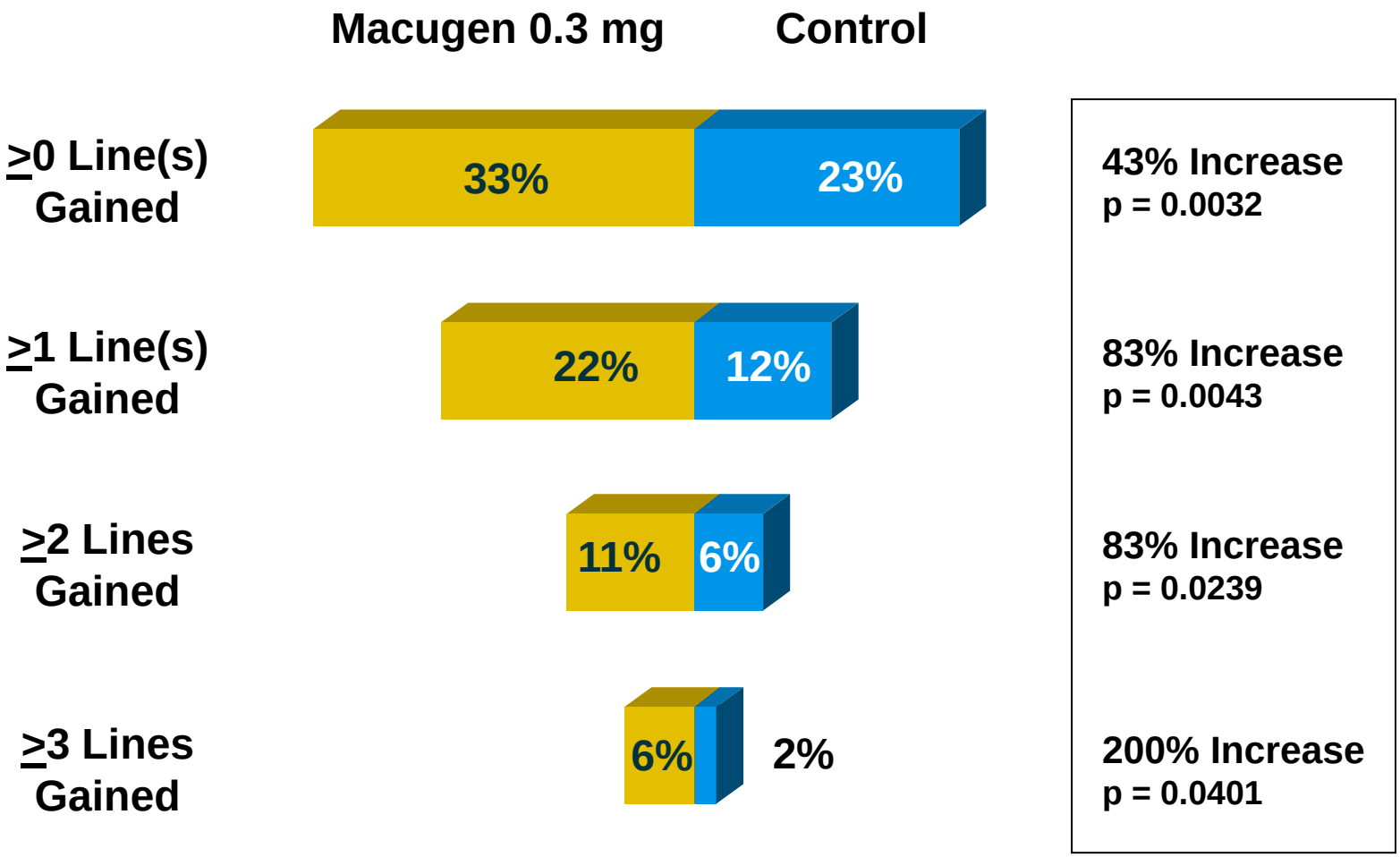
No one subtype drove the effect

Macugen: Course of Therapy

(need information on multiple treatments, why 54-week study period, potential for longer treatment, follow-up)

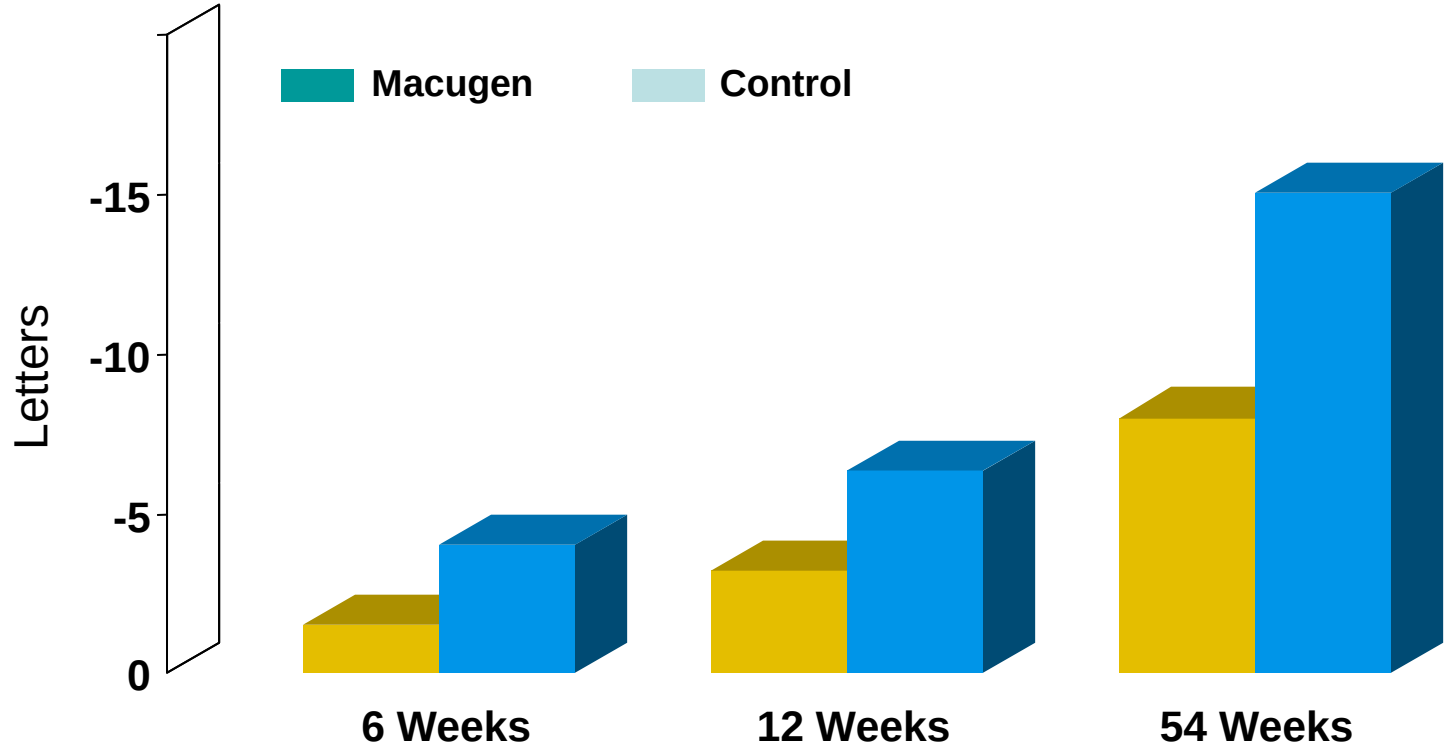
Vision Improvement at 54 Weeks

Secondary and Other Endpoints Support Benefit



Early, Sustained Effect

Mean Change in Visual Acuity



Treatment Effect	**62%**	**49%**	**47%**
p-value	**0.0070**	**0.0038**	**<0.0001**

Macugen Prevented Severe Vision Loss

≥ *6-Line Vision Loss*

Macugen	Sham	Treatment Effect	p- value
10%	22%	55%	<0.0001

Sham patients were more than **twice as likely** to experience ***Severe Vision Loss***

Vision Related Outcomes

- Combined analysis showed that the 0.3 mg dose was statistically significant over sham for:

	P-Value
– Mean 54 week VA change	<0.0001
– Remained at baseline or gained vision	0.001
– Gain of ≥ 15 letters	0.0273
– Mean 6 week VA change	0.0047
– Prevention of severe vision loss – (6 lines or greater)	<0.0001

*P-values conventionally significant and unprotected

High Patient Compliance

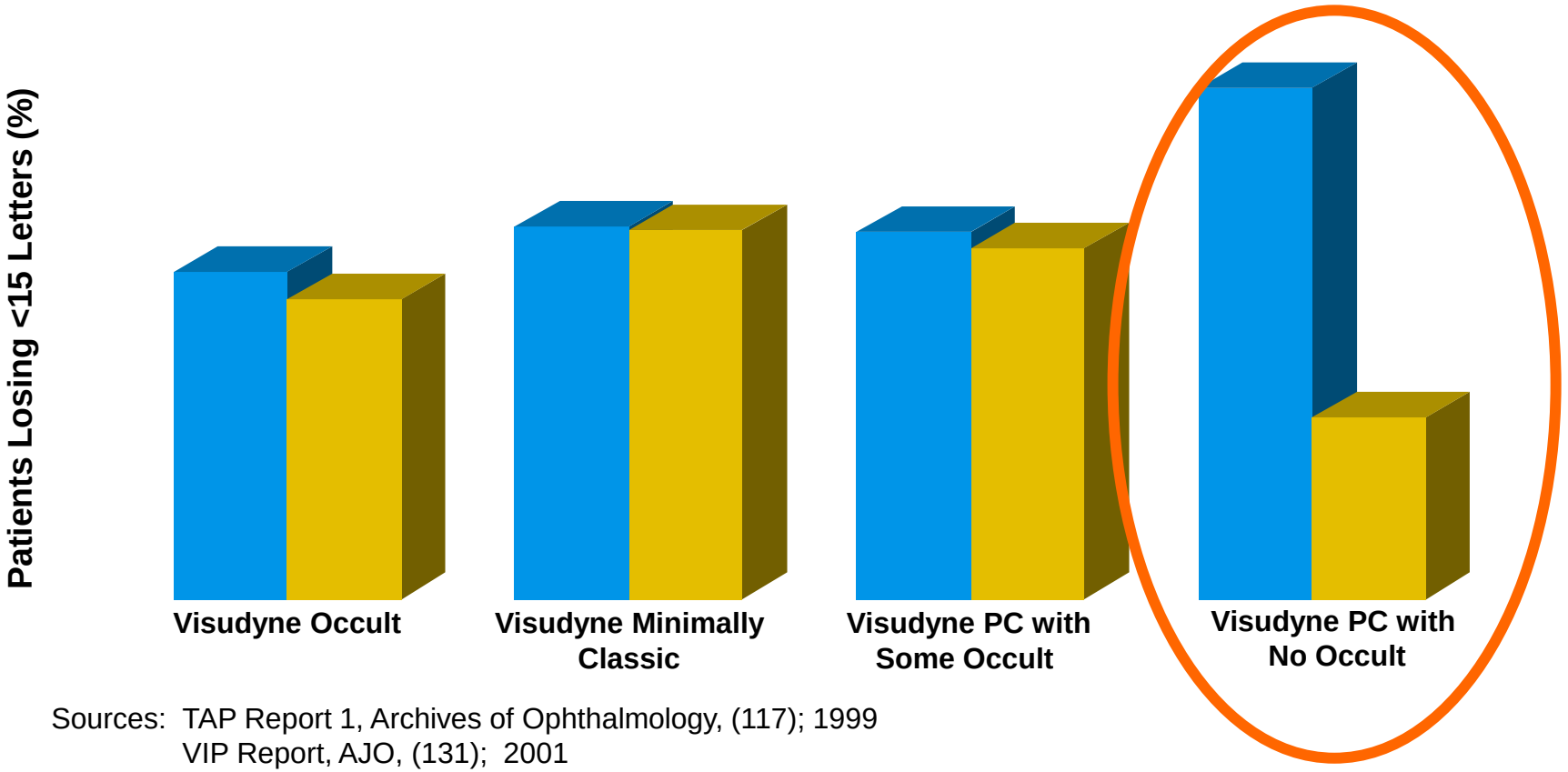
- *Excellent patient motivation*
- *Injection acceptance*

	Macugen	Control
Completed Study	92%	92%
Mean # of Treatments (of 9 maximum treatments)	8.4	8.6

Photodynamic Therapy

Efficacy Limited to a Small Subgroup

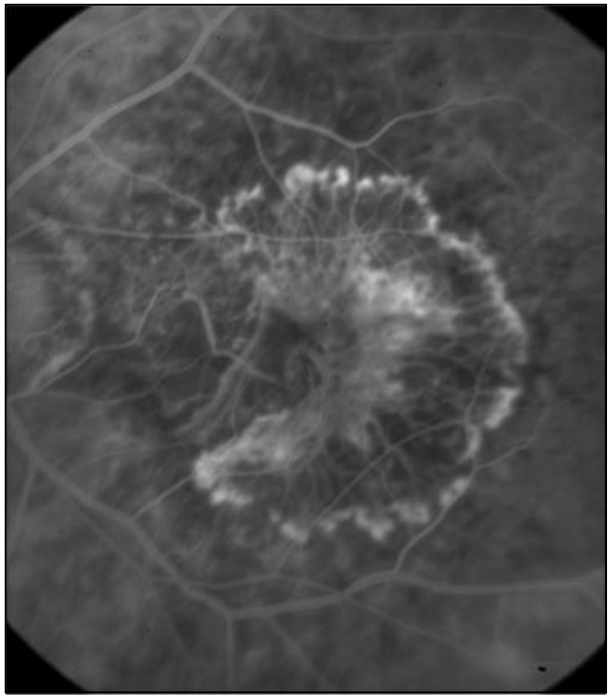
One-year results (TAP and VIP studies)



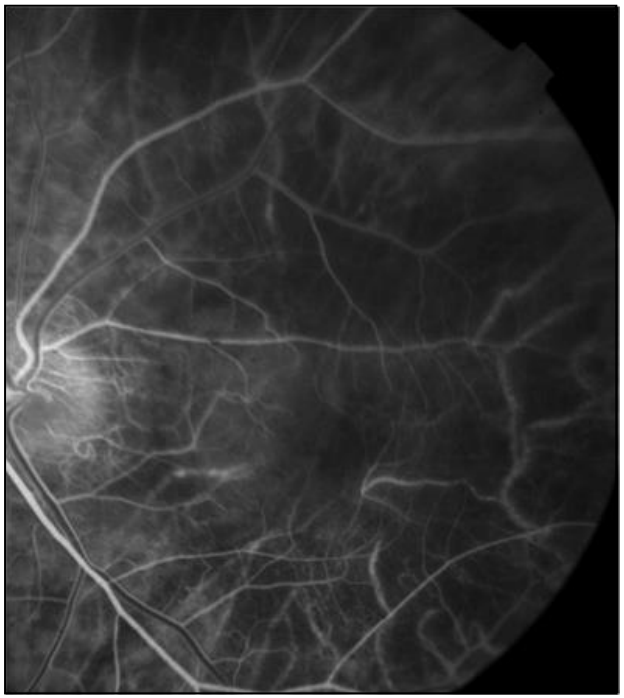
Sources: TAP Report 1, Archives of Ophthalmology, (117); 1999
VIP Report, AJO, (131); 2001

Macugen Effective Against All Subtypes

Predominantly Classic



Baseline

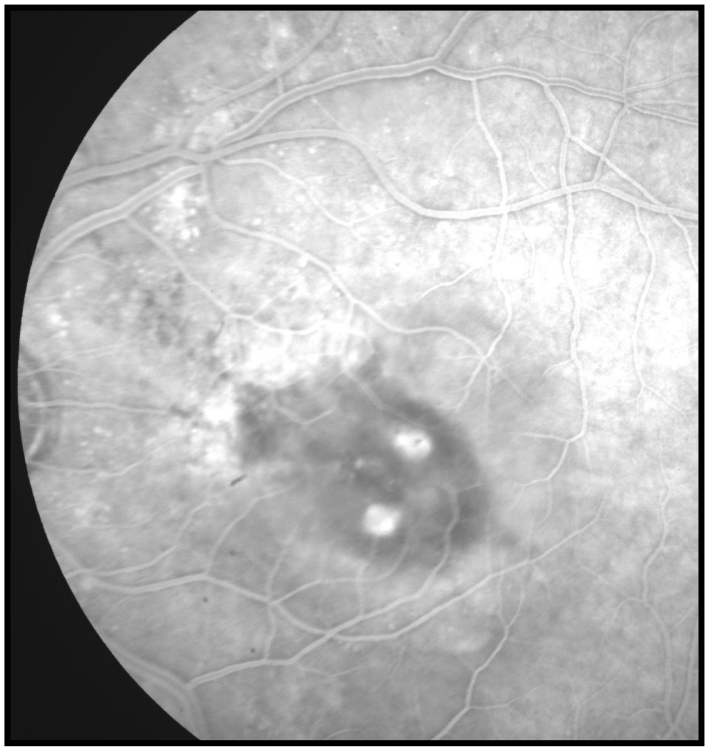


Week 54

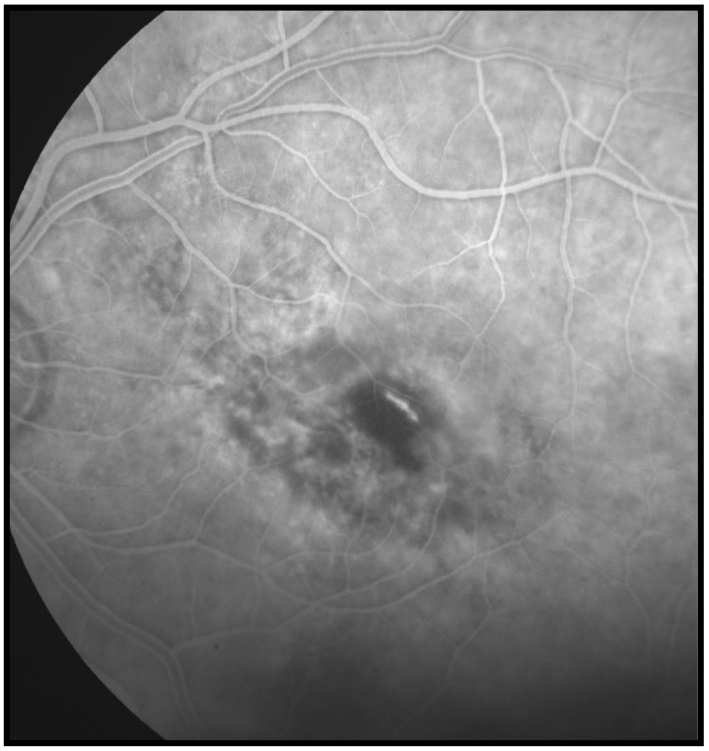
Regression of CNV

Macugen Effective Against All Subtypes

Minimally Classic



Baseline

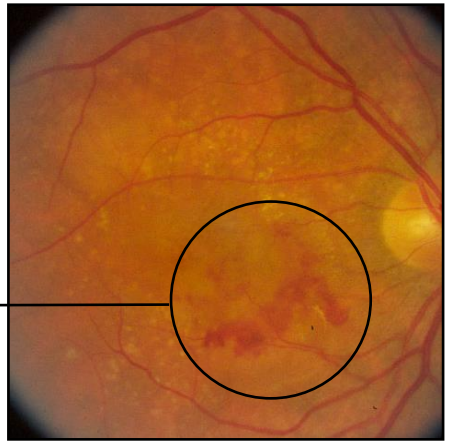


Week 54

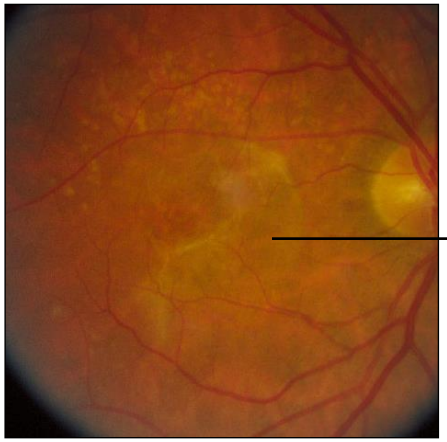
Regression of CNV

Macugen Effective Against All Subtypes

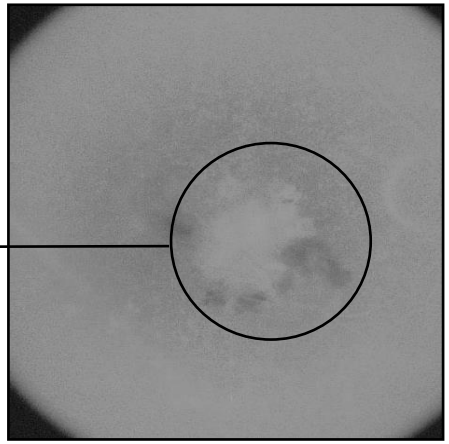
Occult

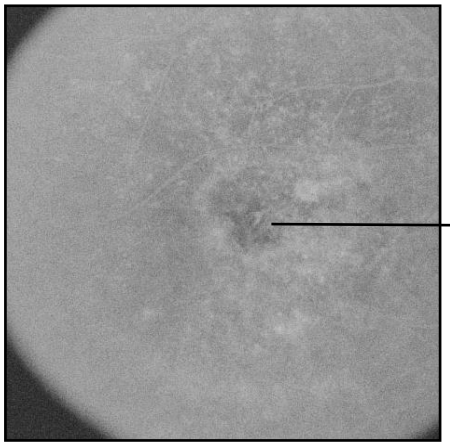


Baseline



Week 54





VISION Conclusions: Efficacy

- Prevents 3- and 6-line vision loss
- Promotes 0, 1-, 2-, 3-line gains
- Across all angiographic subtypes at one year
- Irrespective of lesion size or age
- Against a background of more PDT use in sham
- First ever treatment for minimally classic AMD
- First ever successful trials for occult AMD at 1 year

What about PDT use?

- 25% of all (PC, MC, OC) study patients received PDT

  (prior to study, at baseline, or on-study)
- 64% of PC patients received PDT
- Sham group had higher PDT use than Macugen
- Small sample size limits ability to draw conclusions

However:

- Macugen treatment appears to be independent of Visudyne usage
- Macugen demonstrated strong, statistically significant efficacy despite increased PDT use in sham group

Macugen effect above and beyond Sham + PDT combination

Major Clinical Trials in AMD

- VEGF inhibition: VISION
- PDT therapy: TAP and VIP
- Direct comparisons of the results of separate clinical trials are not valid:
  - Different inclusion criteria
    - Lesion subtype
    - Lesion size
    - Baseline Visual acuity

VISION , TAP and VIP entry criteria

Criteria	VISION	TAP	VIP
Lesion Type	All	Evidence of Classic CNV	Occult (with evidence of recent disease progression)
V.A.	20/40-20/340: (mean xx)	20/40 – 20/200 (mean XX)	20/100 or better (mean XX)
Lesion size	≤ 12 Total Disc Areas (mean XX)	≤ 9 Total Disc Area (mean xx)	≤ 9 Total Disc Areas (mean xx)
Background Therapy	PDT allowed	None	None
Patients	1186	609	339

VISION vs. TAP/VIP

- PDT studies did not allow previous PDT treatments, while VISION did

- More serious pathology, on average, in VISION patients, as measured by lesion size and VA

- VISION study population included all AMD sub-populations, vs. sub-populations in TAP/VIP

SUMMARY: Vision-TAP/VIP Comparison

- Phase II/III VISION trials used broadest entry criteria
- Macugen provides similar, significant treatment benefit across all lesion subtypes
- Macugen improves visual outcomes using multiple, clinically meaningful endpoints
- Favorable systemic safety profile with small number of injection-related side effects consistent with delivery method

Favorable Safety Profile

Local, Targeted Treatment

- No apparent drug-related SAEs
- No apparent systemic safety issues
- Few injection-related SAEs

(n= 7,545 total intravitreal injections)

Events	n	% per Injection	% per patient/yr
Endophthalmitis*	12	0.16	1.3
Lens damage / cataract	5	0.07	0.6
Retinal detachment	5	0.07	0.6

** 9 of 12 endophthalmitis patients remained in the trial*

Intravitreal Injections

- Targets affected tissue
- Extensive experience among retina specialists
- (numbers of procedures done?)
- Well-tolerated (VISION: 92% completed study in treatment and placebo arms)

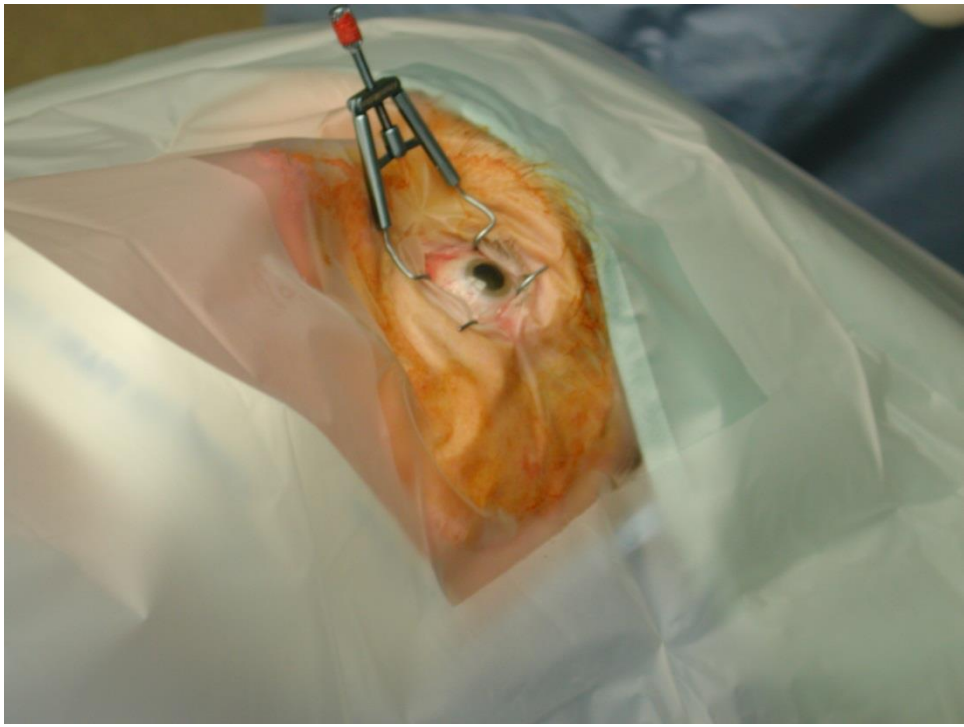
However, intravitreal injections are not without risk

Risks of Intravitreal Injection

- Infection/endophthalmitis
- Retinal detachment
- Lens damage

Infection Prevention

- Preoperative reduction of bacteria on the surface of the eye
  - Povidone-iodine
  - Antibiotics
- Isolation of the surgical field
- Aseptic technique
- Postoperative use of antibiotics



Safety Summary

- Intravitreal injections are associated with low incidence of endophthalmitis
- Ocular surface bacteria are the most common sources of infections
- Goal: eliminate bacteria from the ocular surface
  - Preoperative 5% povidone-iodine prep – consider irrigation of fornices
  - Preoperative and postoperative use of topical antibiotics – consider qid dosing x 3 days prior
  - Proper aseptic technique
    - Speculum
    - drape

Macugen Fulfills AMD Therapy Unmet Needs

- Benefit all patients with wet AMD
- Halt or reverse disease progression
- Mechanistically precise, rational therapy
- No drug-related SAEs
- Limited bystander cell damage

- “Ideal” delivery vehicle: drops/ointment.
- For now, safer injections by reducing eliminating bacteria from ocular surface