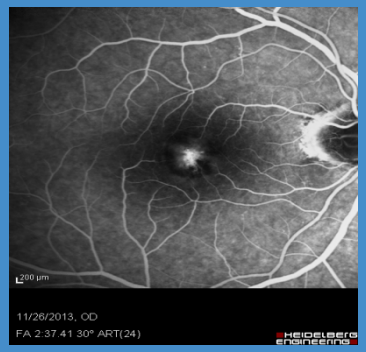
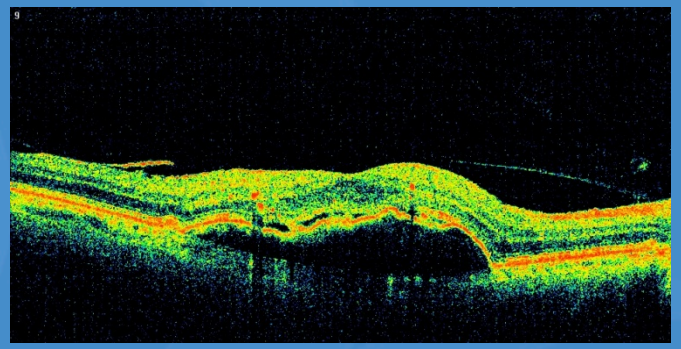
Aflibercept

Επαναπροσδιορίζοντας την Αποτελεσματικότητα της αντι-VEGF Θεραπείας στην Εξιδρωματική ΗΕΩ





Αλέξανδρος Χαρώνης, MD

Τμήμα Αμφιβληστροειδούς & Οφθαλμικών Φλεγμονών

Ιατρικό Κέντρο Οφθαλμολογίας Athens Vision

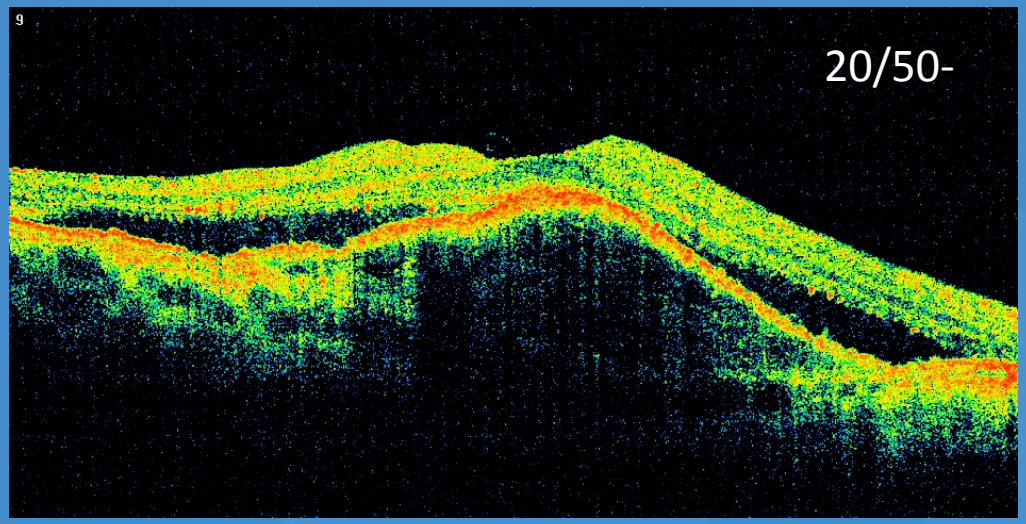
1η Επιστημονική Ημερίδα GVRS, Αθήνα 3/5/2014

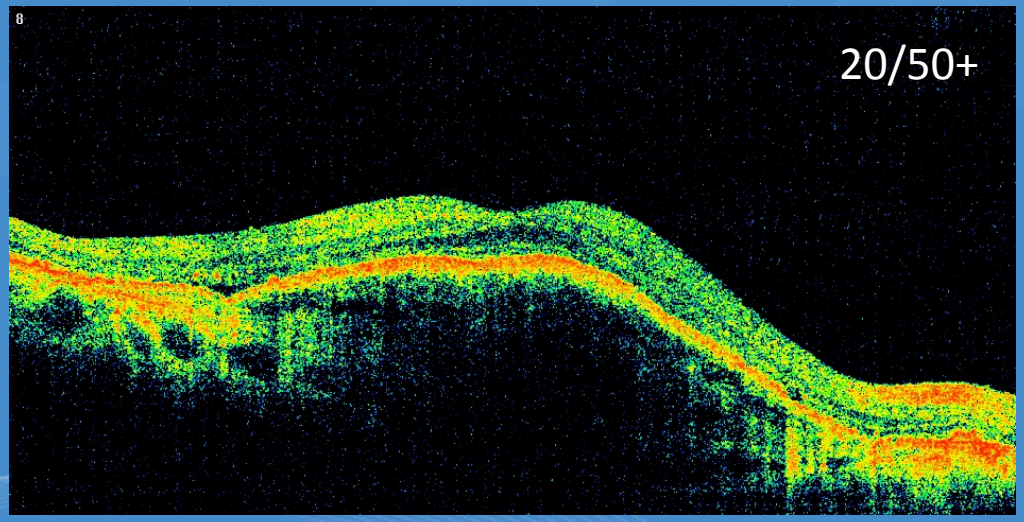
Athens Vision

Financial Disclosures

Allergan – Consultant, Advisor, Lecturer
Bayer – Lecturer, Research
Novartis – Consultant, Advisor, Lecturer, Research

Τί σημαίνει αποτελεσματική αντι-VEGF Rx;





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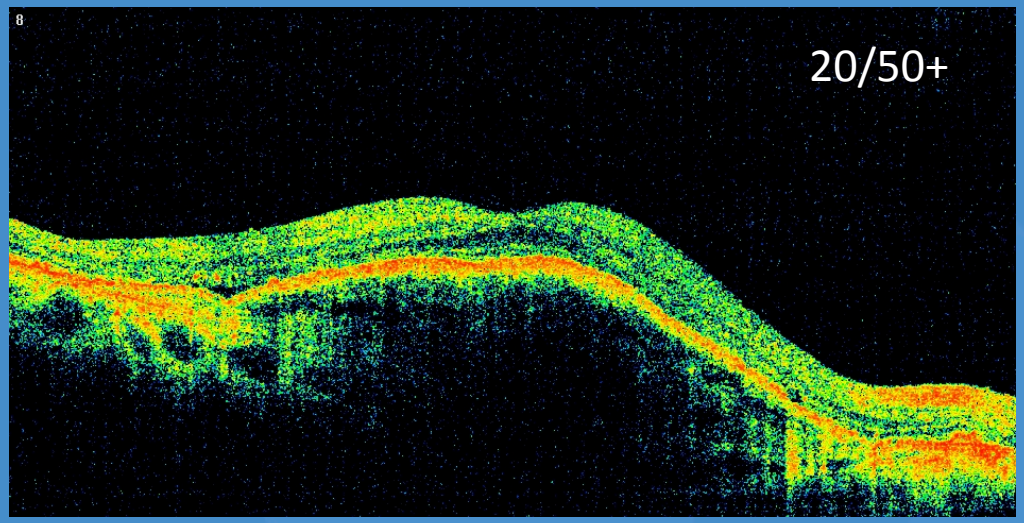
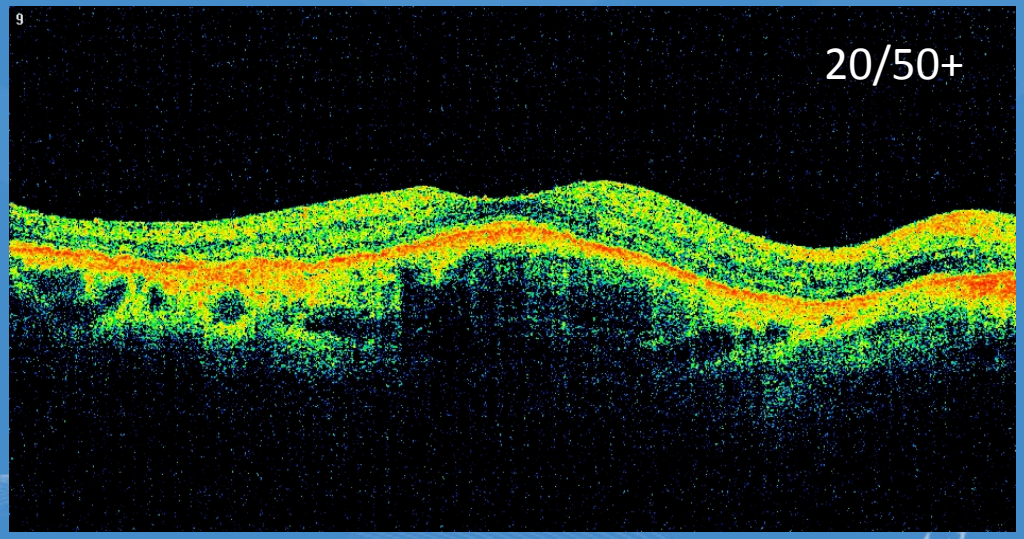
Τί σημαίνει αποτελεσματική αντι-VEGF Rx;





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Το Πρόβλημα…
AMD: Worldwide Prevalence is 31.9 Million[1]

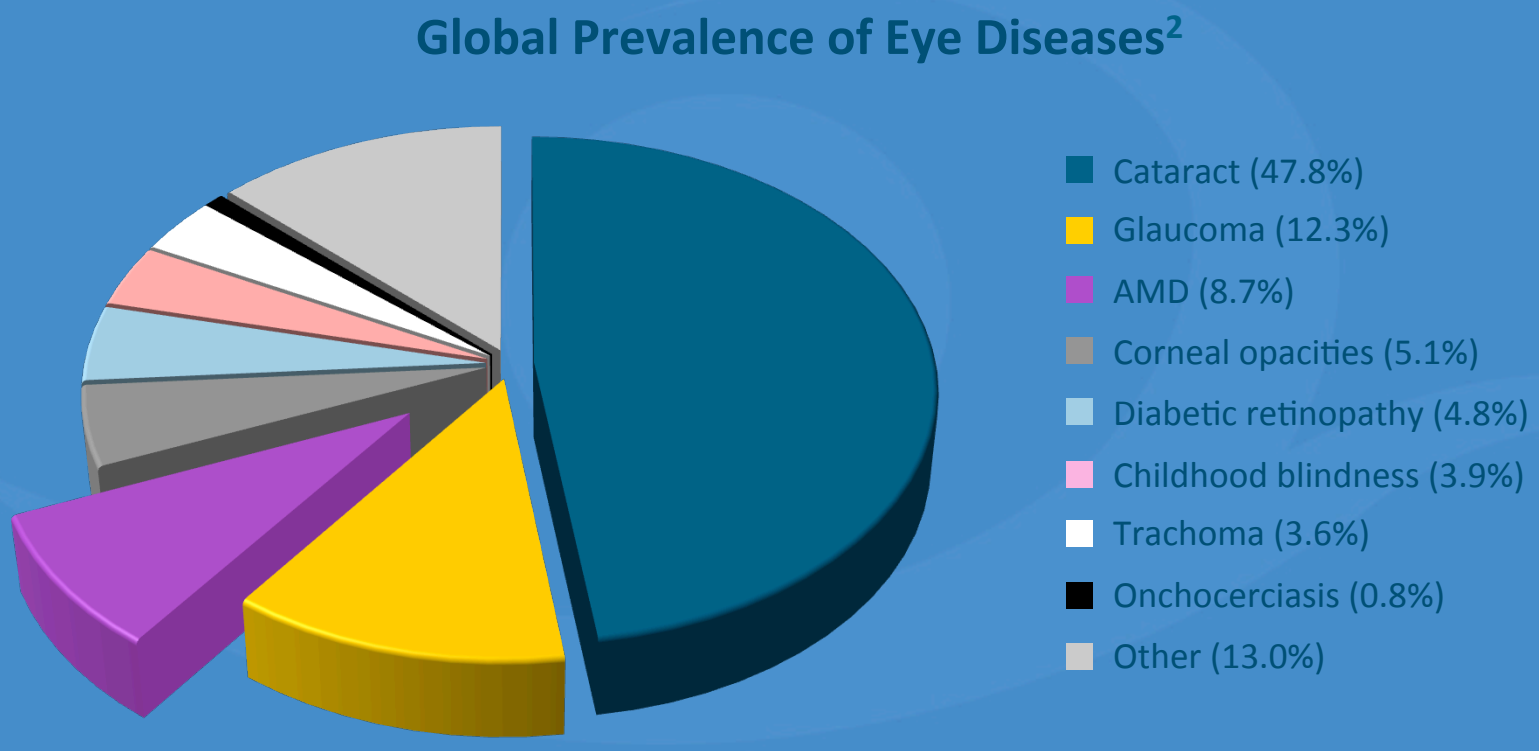


Figure adapted from Resnikoff S et al. *Bulletin of the World Health Organization.* 2004.[1]

1. World Health Organization. *The Global Burden of Disease: 2004 Update*. Geneva, Switzerland; 2008.
2. Resnikoff S et al. *Bulletin of the World Health Organization.* 2004;82(11):844-851.

AMD: Prevalence Predicted to Increase With Growth of Aging Population[1–2]

By 2050:

- Estimated world population will be 8.9 billion[3]
- Life expectancy will have risen from 64.6 years to 74.3 years[3]
- AMD population globally will be **46.9 million**[3,a]

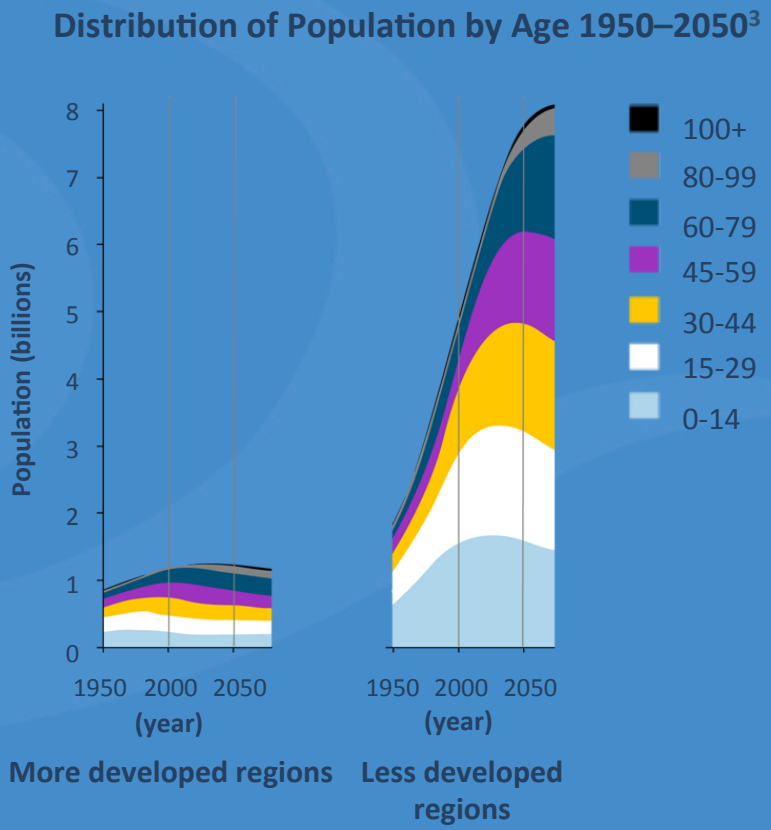


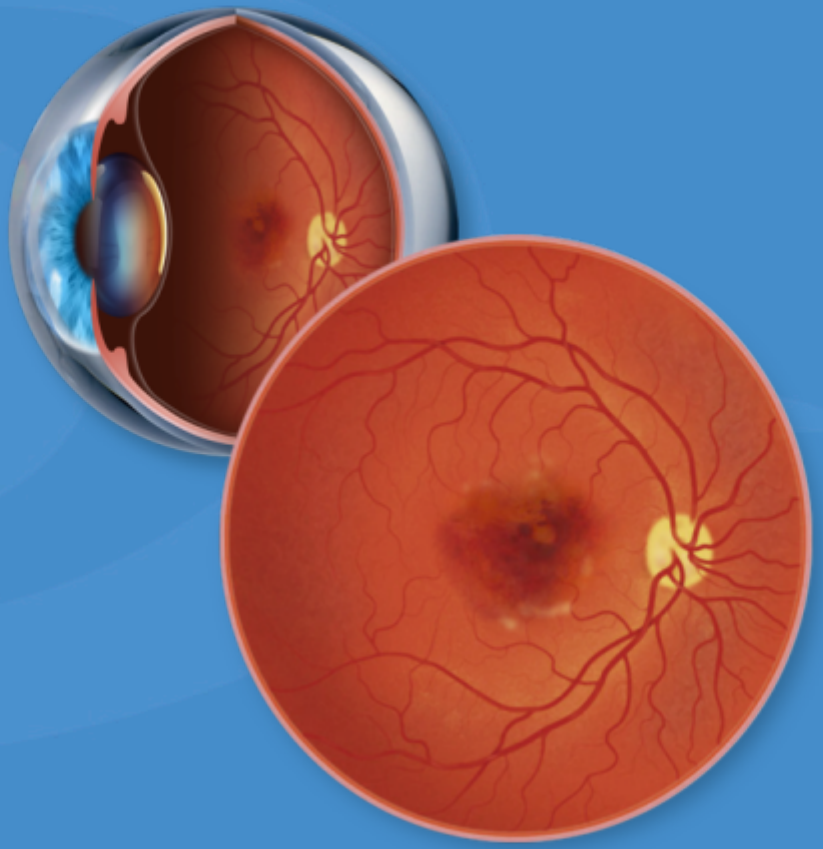
Figure adapted from United Nations. *World Population to 2300*. 2004.[3]

[a]Estimation based on projected 47% population growth.[3]

1. West S, Sommer A. *Bulletin of the World Health Organization*. 2001;79(3):244-248.
2. Resnikoff S et al. *Bulletin of the World Health Organization.* 2004;82(11):844-851.
3. United Nations. *World Population to 2300*. New York, NY; 2004.

Wet AMD ~ 90% of Severe Vision Loss Due to AMD[1]

- Characterized by[2]
  - **Subretinal fluid**
  - **Subretinal hemorrhage**
  - **RPE detachment**
  - **Hard exudates**
- Can be effectively treated with anti-angiogenic therapies[2]

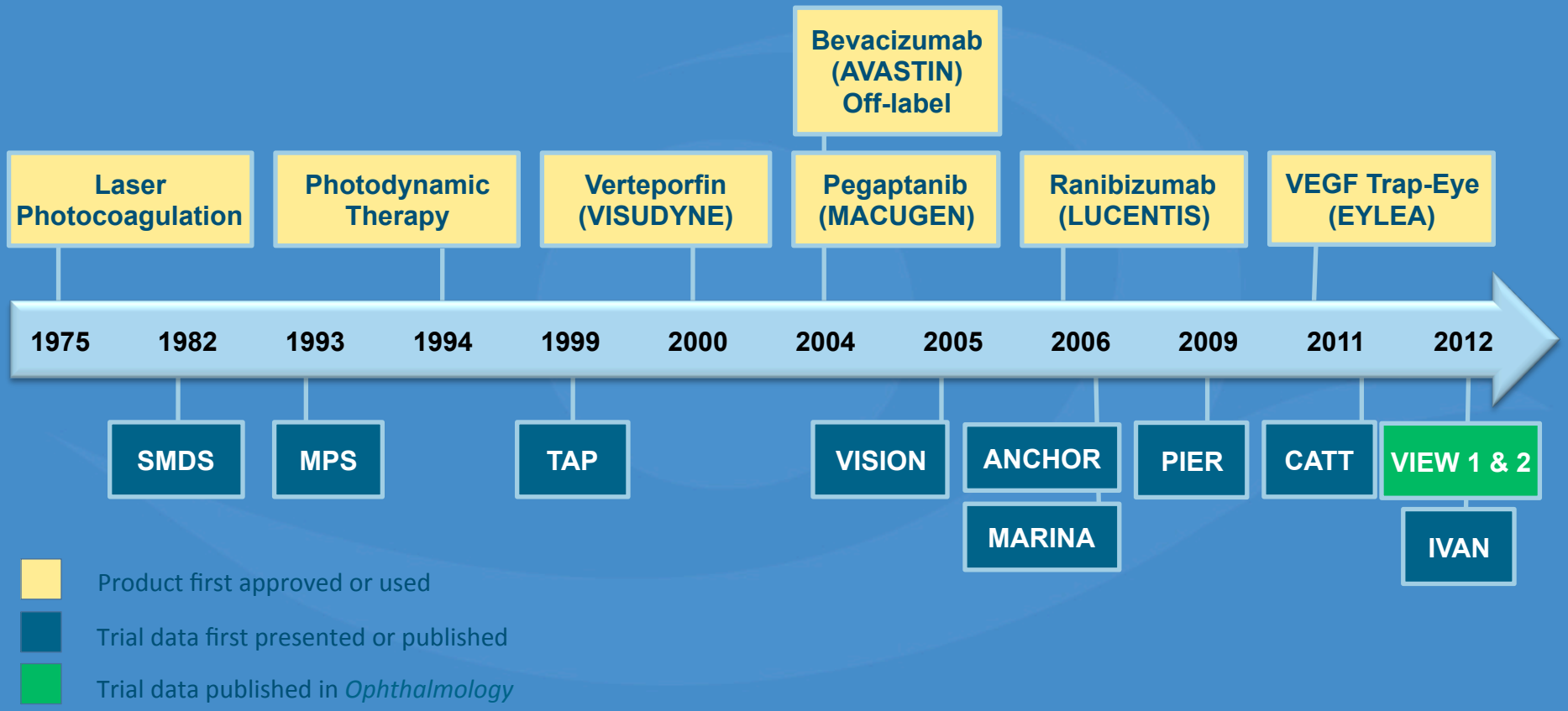


Wet AMD in the central retina

Image courtesy of Bayer HealthCare

1. Preferred Practice Pattern® Guidelines. American Academy of Ophthalmology; 2011.
2. Lim JI, Tsong JW. In: *Age-Related Macular Degeneration.* 2007:125-157.

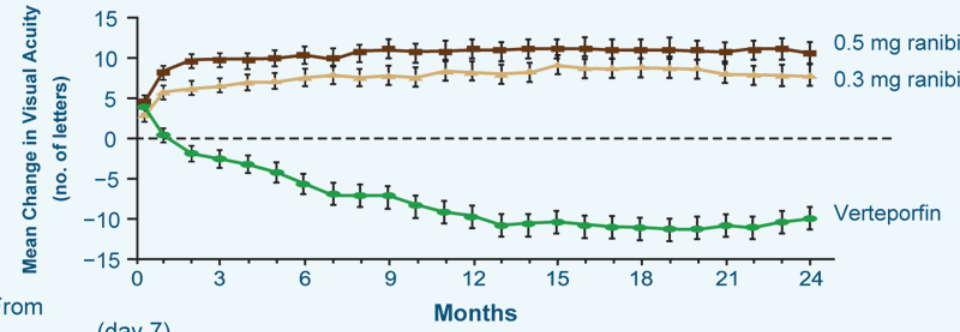
wet AMD: Milestones in Treatment



ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; CATT = Comparisons of Age-Related Macular Degeneration Treatments Trials; IVAN = A Randomised Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; MPS = Macular Photocoagulation Study Group; PIER = Phase IIIb, Multi-center, Randomized, Double-Masked, Sham Injection-Controlled Study of Efficacy and Safety of Ranibizumab in Subjects With Subfoveal CNV With or Without Classic CNV Secondary to AMD; SMDS = Senile Macular Degeneration Study; TAP = Treatment of AMD With Photodynamic Therapy; VIEW 1 & 2 = Vascular Endothelial Growth Factor Trap-Eye for Neovascular Age-Related Macular Degeneration; VISION = VEGF Inhibition Study in Ocular Neovascularization.

ANCHOR[1] and MARINA[2]: Mean Change From Baseline Visual Acuity Improved With Ranibizumab

ANCHOR[1]

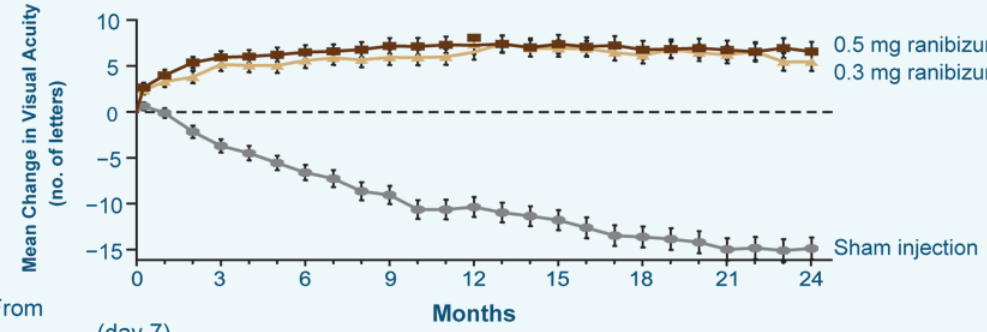


Mean Change From Baseline	(day 7)								
0.5 mg of ranibizumab	+4.6	+10.0	+10.6	+11.4	+11.3	+11.4	+11.1	+10.9	+10.7
0.3 mg of ranibizumab	+2.9	+6.8	+7.9	+8.1	+8.5	+9.4	+9.2	+8.4	+8.1
Verteporfin	+3.9	−2.5	−5.6	−7.2	−9.6	−10.4	−11.2	−10.7	−9.8

Both comparisons $P<0.001$ vs verteporfin

Figure adapted from Brown DM et al; ANCHOR Study Group. *Ophthalmology*. 2009.[1]

MARINA[2]



Mean Change From Baseline	(day 7)								
0.5 mg of ranibizumab	+2.6	+5.9	+6.5	+7.2	+7.2	+7.4	+6.8	+6.7	+6.6
0.3 mg of ranibizumab	+2.3	+5.1	+5.6	+5.9	+6.5	+6.9	+6.1	+6.2	+5.4
Sham injection	+0.6	−3.7	−6.6	−9.1	−10.4	−11.8	−13.6	−15.0	−14.9

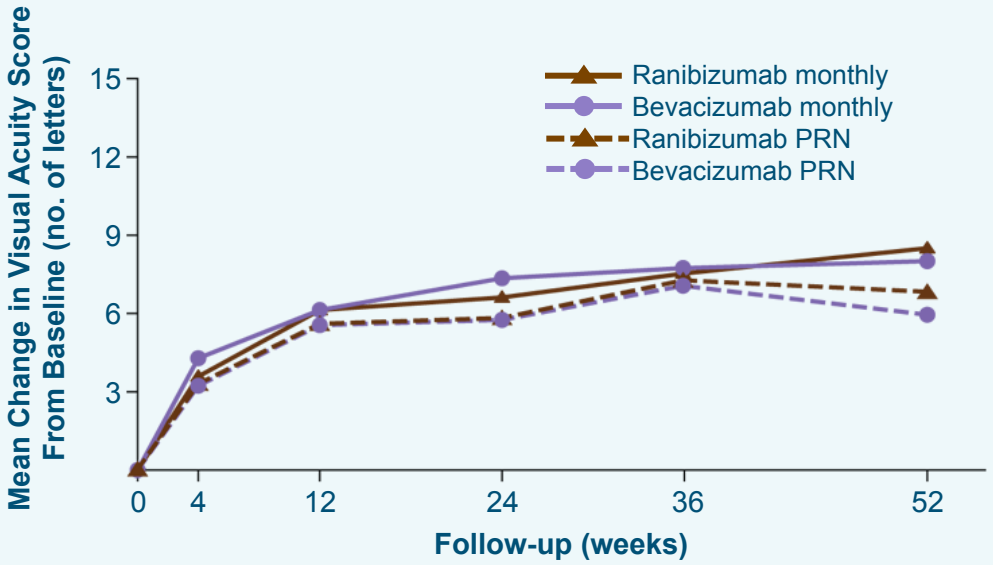
Both comparisons $P<0.001$ vs sham

Figure adapted from Rosenfeld PJ et al; MARINA Study Group. *N Engl J Med*. 2006.[2]

1. Brown DM et al; ANCHOR Study Group. *Ophthalmology*. 2009;116:57-65.
2. Rosenfeld PJ et al; MARINA Study Group. *N Engl J Med*. 2006;355(14):1419-1431.

CATT: Visual Acuity Improved From Baseline to 1 Year in All Treatment Groups[1]

- Most of the improvement occurred during the first 6 months



(*P*=0.16)

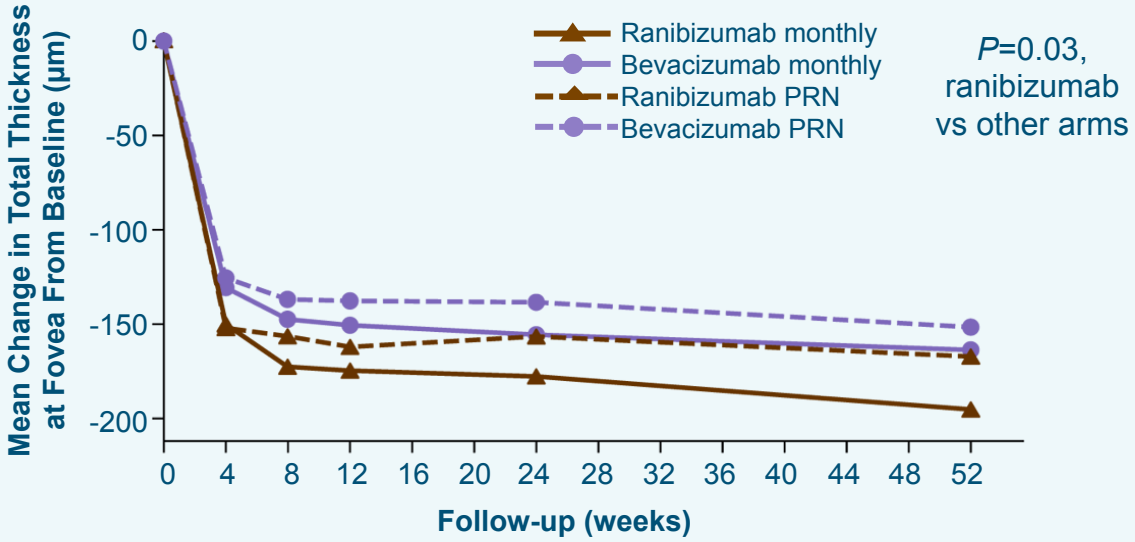
Mean (±SE) Change in Visual Acuity Score From Baseline (no. of letters)					
Ranibizumab monthly	+3.6±0.5	+6.1±0.7	+6.6±0.8	+7.5±0.9	+8.5±0.8
Bevacizumab monthly	+4.3±0.6	+6.1±0.7	+7.3±0.9	+7.7±1.0	+8.0±1.0
Ranibizumab PRN	+3.3±0.6	+5.6±0.7	+5.8±0.7	+7.2±0.7	+6.8±0.8
Bevacizumab PRN	+3.2±0.5	+5.6±0.7	+5.8±0.8	+7.1±0.9	+5.9±1.0

Figure adapted from Martin DF et al; CATT Research Group. *N Engl J Med.* 2011.

1. Martin DF et al; CATT Research Group. *N Engl J Med.* 2011;364(20):1897-1908.

CATT: Monthly Ranibizumab Offered the Greatest Reductions in CRT and Fluid[1]

- The proportion of patients with no fluid on OCT ranged from **19.2%** (bevacizumab PRN) to **43.7%** (ranibizumab monthly) (*P*<0.001)



Mean (±SE) Change in Thickness at Fovea From Baseline (µm)	Wk 4	Wk 8	Wk 12	Wk 24	Wk 52
Ranibizumab monthly	−151±9	−173±9	−175±10	−178±10	−196±11
Bevacizumab monthly	−131±9	−147±9	−151±10	−156±11	−164±11
Ranibizumab PRN	−153±9	−157±10	−163±11	−157±11	−168±11
Bevacizumab PRN	−126±8	−137±9	−138±10	−139±10	−152±11

CRT = central retinal thickness.

Figure adapted from Martin DF et al; CATT Research Group. *N Engl J Med.* 2011.[1]

1. Martin DF et al; CATT Research Group. *N Engl J Med.* 2011;364(20):1897-1908.

VEGF Trap-Eye: Specifically Designed to Block Members of the VEGF Family

- **Fully human fusion protein**[1]
  - Human VEGF-R1 and VEGF-R2 domains and human IgG1 Fc
- Traps all VEGF-A isoforms and PlGF[2]
- Higher affinity than native receptors[2]
- Strict 1:1 binding[2]
- Formulated for intravitreal injection[3]
  - Iso-osmotic solution
  - Highly purified

VEGF Trap Development and Structure

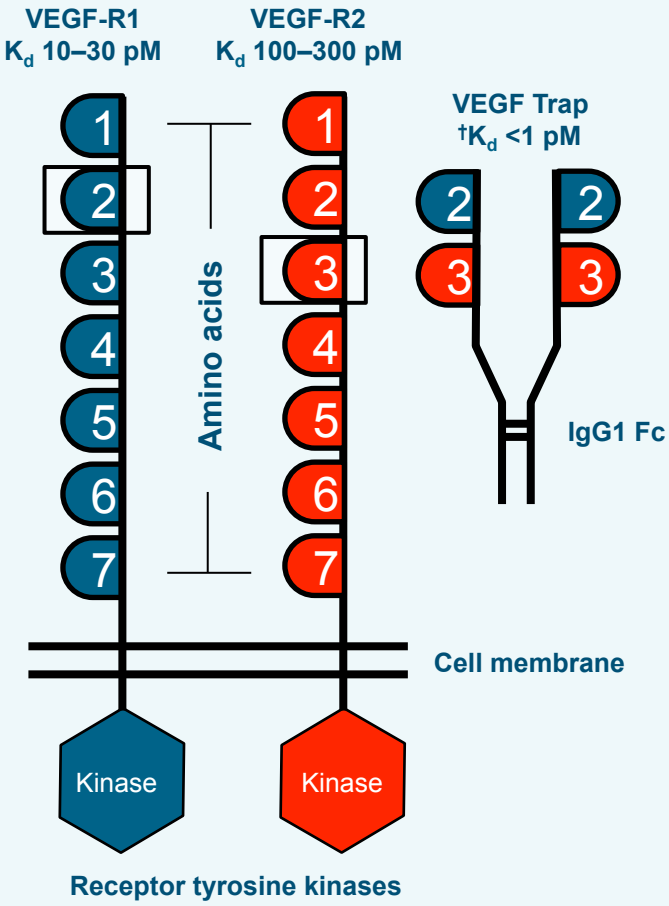


Figure adapted from Dixon JA et al. *Expert Opin Investig Drugs.* 2009.[4]

Fc = fragment crystallizable/constant region; K_d = dissociation constant.

1. Holash J et al. *Proc Natl Acad Sci U S A.* 2002;99(17):11393-11398.
2. Heier JS. *Retinal Physician*. 2009. http://www.retinalphysician.com.
3. Stewart MY. *Br J Ophthalmol.* 2012;96(9):1157-1158.
4. Dixon JA et al. *Expert Opin Investig Drugs.* 2009;18(10):1573-1580.

VEGF Trap-Eye Binds VEGF Dimer on Both Sides[1] "Like a Trap"

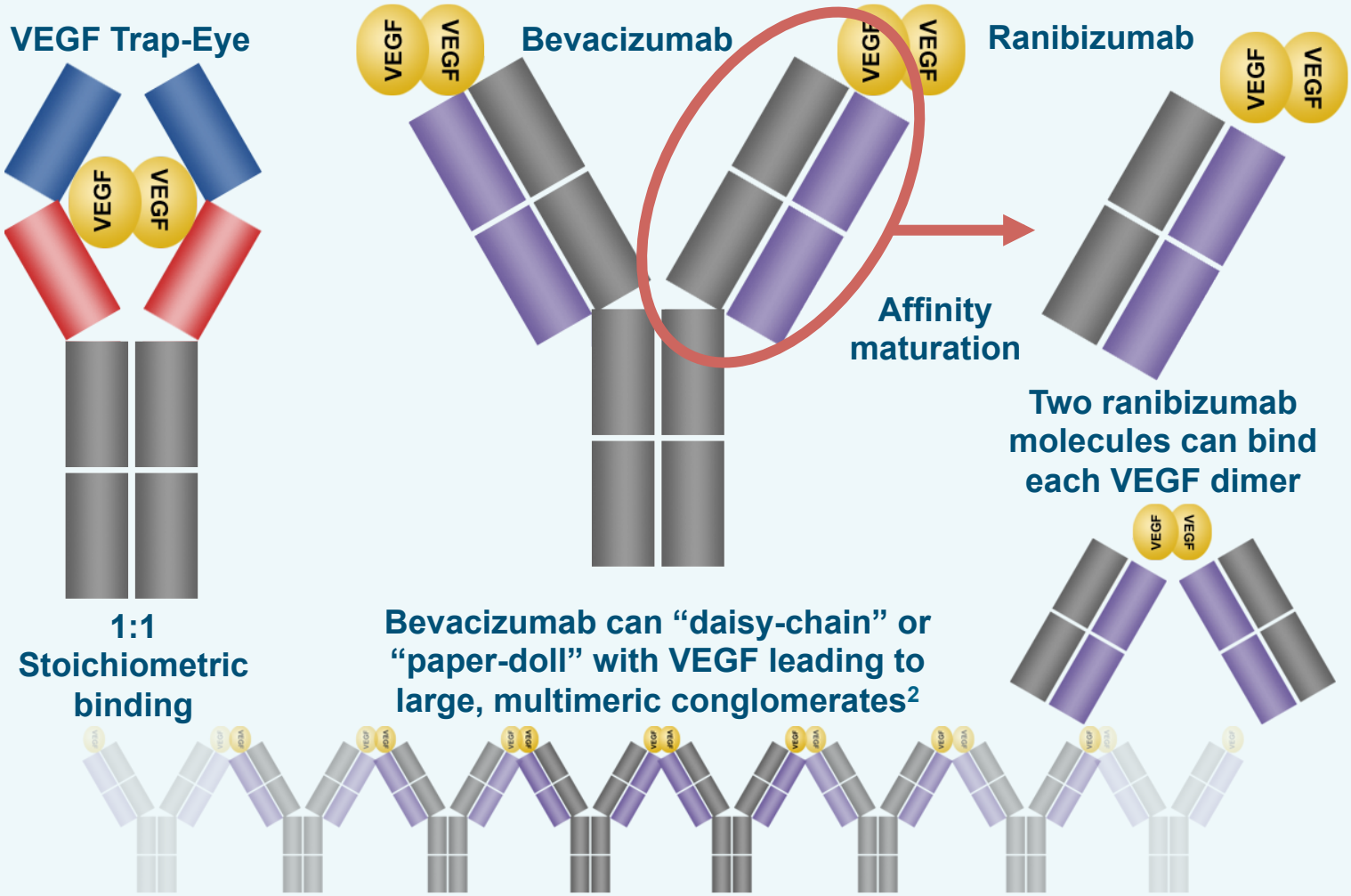


Image courtesy of Bayer HealthCare

1. Heier JS. *Retinal Physician*. 2009. http://www.retinalphysician.com.
2. Zhang A et al. *Pharm Res*. 2012;29(1):236-250.

Mathematical Modeling of Intravitreal Activity of VEGF Trap-Eye

- The predicted, time-dependent intravitreal biological activity of 0.5 mg ranibizumab at 30 days is comparable to the predicted activity of 1.15 mg VEGF Trap-Eye at 79 days post-injection and comparable to activity of 4.0 mg VEGF Trap-Eye at 87 days after injection[1]

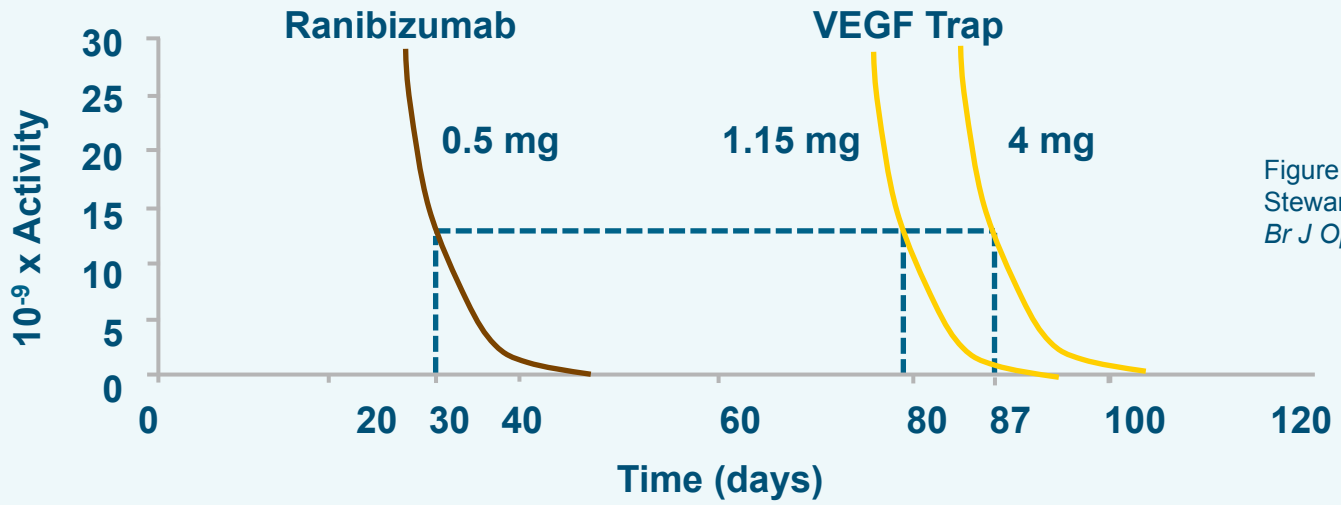
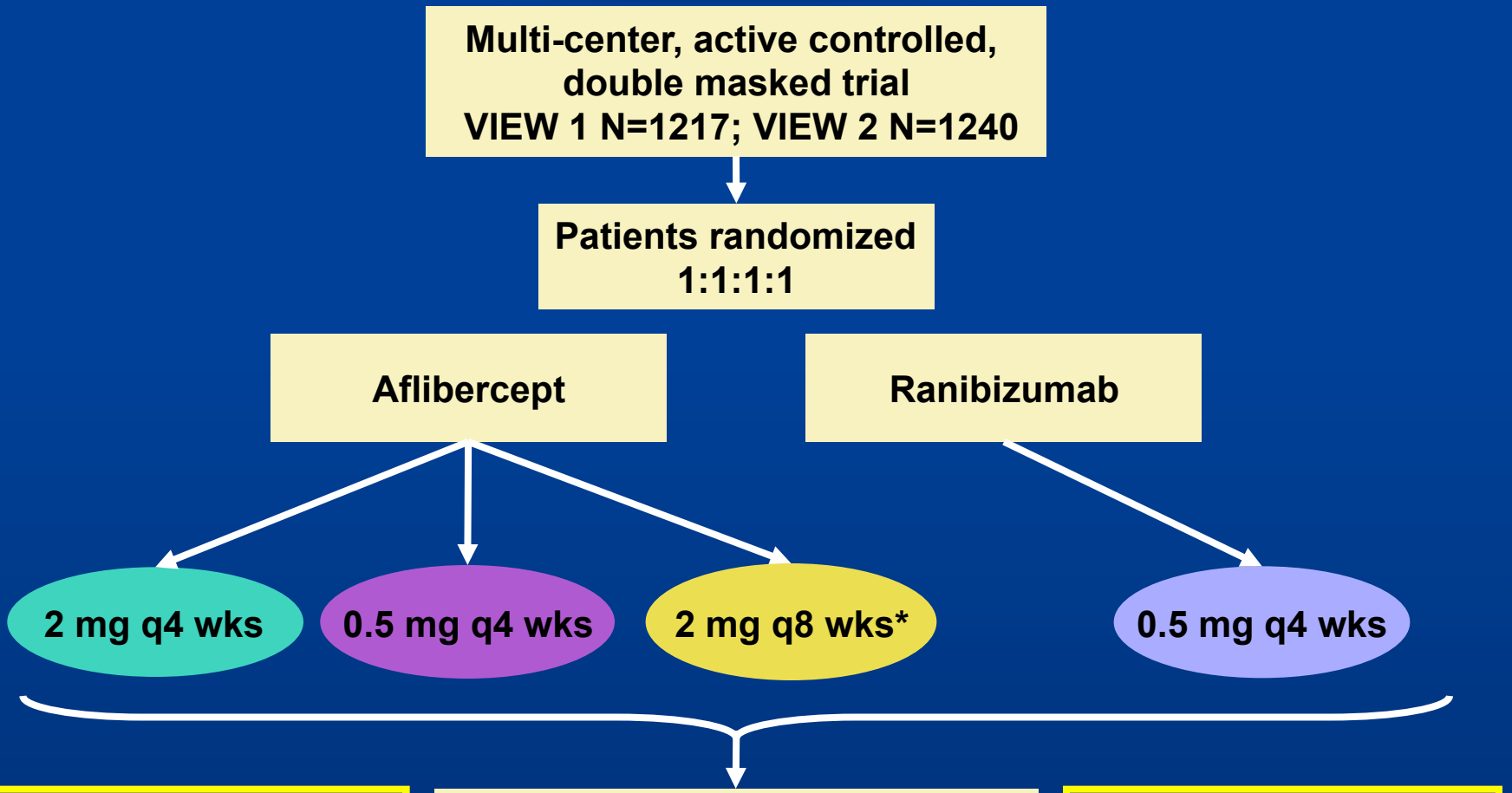


Figure adapted from Stewart MW, Rosenfeld PJ. *Br J Ophthalmol.* 2008.[1]

- The intravitreal half-lives of ranibizumab, bevacizumab, and VEGF Trap-Eye were estimated to be 3.2, 5.6, and 4.8 days, respectively[2]

1. Stewart MW, Rosenfeld PJ. *Br J Ophthalmol.* 2008;92(3):667-668.
2. Stewart MW et al. *Retina*. 2012;32(3):434-457.

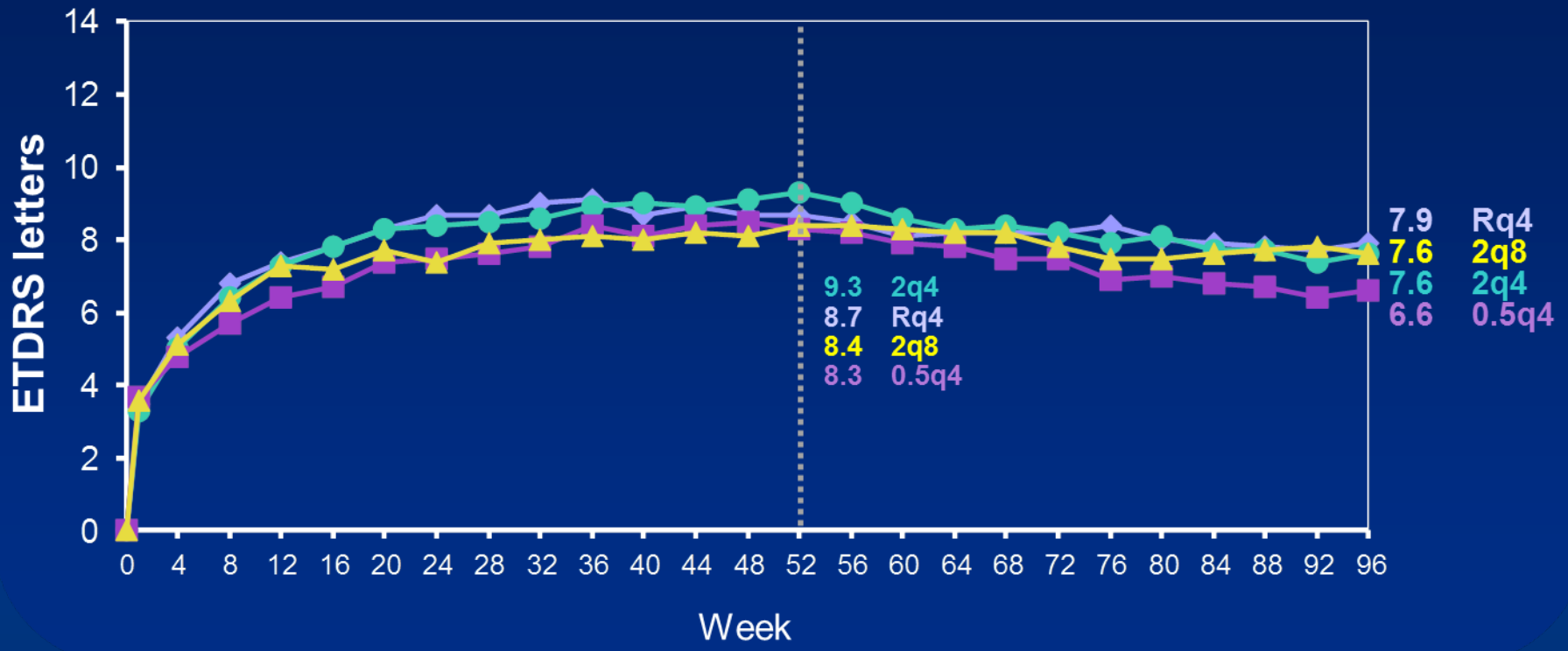
VIEW - Study Design



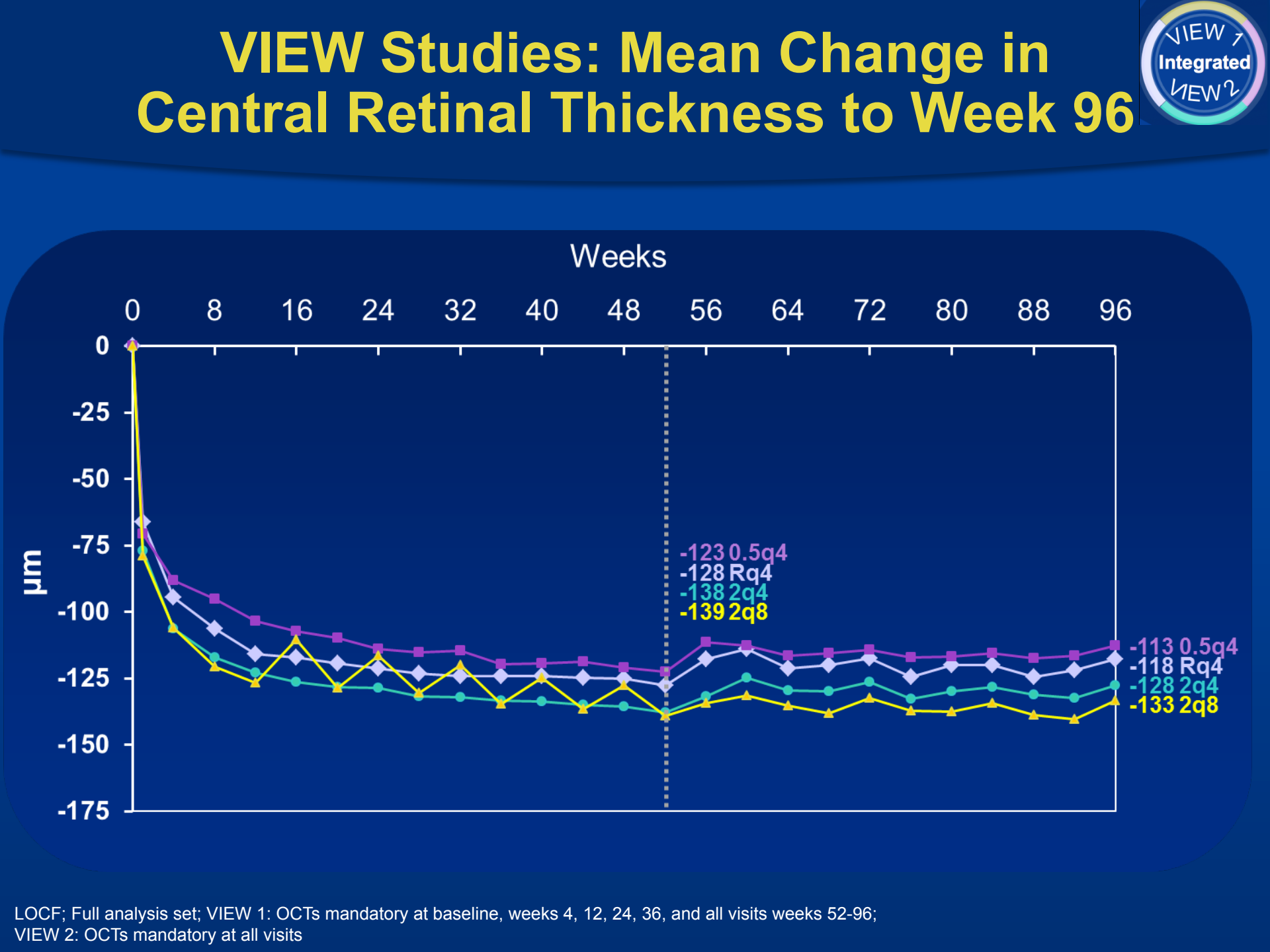
*After 3 initial monthly doses

With additional evaluation visits

VIEW Studies: Mean Change in Visual Acuity Baseline to Week 96



VIEW Studies: Mean Change in Central Retinal Thickness to Week 96



LOCF; Full analysis set; VIEW 1: OCTs mandatory at baseline, weeks 4, 12, 24, 36, and all visits weeks 52-96;
VIEW 2: OCTs mandatory at all visits

VIEW Studies: Patients With Study Eye Ocular SAEs Over 96 Weeks

	RBZ 0.5q4	IVT-AFL 2q4	IVT-AFL 0.5q4	IVT-AFL 2q8	All IVT-AFL
N (safety analysis set)	595	613	601	610	1824
# subjects w/at least 1 AE n(%)	26 (4.4%)	22 (3.6%)	19 (3.2%)	24 (3.9%)	65 (3.6%)
Cataract	1 (0.2%)	4 (0.7%)	3 (0.5%)	4 (0.7%)	11 (0.6%)
Macular degeneration	0	0	0	2 (0.3%)	2 (0.1%)
Macular hole	0	0	2 (0.3%)	0	2 (0.1%)
Posterior capsule opacification	2 (0.3%)	0	0	0	0
Retinal detachment	3 (0.5%)	1 (0.2%)	2 (0.3%)	0	3 (0.2%)
Retinal haemorrhage	4 (0.7%)	3 (0.5%)	5 (0.8%)	5 (0.8%)	13 (0.7%)
Retinal pigment epithelial tear	1 (0.2%)	0	1 (0.2%)	3 (0.5%)	4 (0.2%)
Visual acuity reduced	5 (0.8%)	4 (0.7%)	3 (0.5%)	7 (1.1%)	14 (0.8%)
Endophthalmitis	5 (0.8%)	4 (0.7%)	1 (0.2%)	0	5 (0.3%)
Intraocular pressure increased	1 (0.2%)	0	1 (0.2%)	2 (0.3%)	3 (0.2%)

Events occurring in ≥2 patients

VIEW Studies: Patients With Non-Ocular SAEs Over 96 Weeks

	RBZ 0.5q4	IVT-AFL 2q4	IVT-AFL 0.5q4	IVT-AFL 2q8	All IVT-AFL
N (safety analysis set)	**595**	**613**	**601**	**610**	**1824**
# subjects w/at least 1 AE n(%)	**146 (24.5%)**	**131 (21.4%)**	**152 (25.3%)**	**154 (25.2%)**	**437 (24.0%)**
Cardiac disorders	39 (6.6%)	31 (5.1%)	34 (5.7%)	42 (6.9%)	107 (5.9%)
Gastrointestinal disorders	17 (2.9%)	11 (1.8%)	18 (3.0%)	19 (3.1%)	48 (2.6%)
General disorders and administration site conditions	9 (1.5%)	9 (1.5%)	7 (1.2%)	5 (0.8%)	21 (1.2%)
Hepatobiliary disorders	5 (0.8%)	7 (1.1%)	6 (1.0%)	2 (0.3%)	15 (0.8%)
Infections and infestations	36 (6.1%)	23 (3.8%)	24 (4.0%)	36 (5.9%)	83 (4.6%)
Injury, poisoning and procedural complications	17 (2.9%)	23 (3.8%)	23 (3.8%)	32 (5.2%)	78 (4.3%)
Metabolism and nutrition disorders	7 (1.2%)	7 (1.1%)	7 (1.2%)	5 (0.8%)	19 (1.0%)
Musculoskeletal and connective tissue disorders	11 (1.8%)	10 (1.6%)	9 (1.5%)	11 (1.8%)	30 (1.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23 (3.9%)	19 (3.1%)	35 (5.8%)	27 (4.4%)	81 (4.4%)
Nervous system disorders	15 (2.5%)	24 (3.9%)	20 (3.3%)	22 (3.6%)	66 (3.6%)
Renal and urinary disorders	2 (0.3%)	9 (1.5%)	4 (0.7%)	7 (1.1%)	20 (1.1%)
Respiratory, thoracic and mediastinal disorders	12 (2.0%)	12 (2.0%)	11 (1.8%)	15 (2.5%)	38 (2.1%)
Vascular disorders	12 (2.0%)	10 (1.6%)	12 (2.0%)	12 (2.0%)	34 (1.9%)

SOC ≥1%

VIEW Studies
APTC Events Over 96 Weeks

	RBZ 0.5q4	IVT-AFL 2q4	IVT-AFL 0.5q4	IVT-AFL 2q8	All IVT-AFL
N (safety analysis set)	595	613	601	610	1824
Any APTC event	19 (3.2%)	15 (2.4%)	23 (3.8%)	22 (3.6%)	60 (3.3%)
Vascular deaths	3 (0.5%)	5 (0.8%)	8 (1.3%)	11 (1.8%)	24 (1.3%)
Non-fatal MI	12 (2.0%)	6 (1.0%)	12 (2.0%)	7 (1.1%)	25 (1.4%)
Non-fatal stroke	5 (0.8%)	5 (0.8%)	3 (0.5%)	5 (0.8%)	13 (0.7%)

Συστηματική Ασφάλεια
"Post Clinical Trial" Data

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EPAR Public Assessment Report for Eylea

>85 ετών AEE **7%** (20) vs **1.5%** (1) στο 1ο έτος
9.5% (27) vs **3.5%** (3) στα 2 έτη

SAILOR interim 6 month analysis

AEE 0.5mgR **1.2%** vs **0.3%** 0.3mgR

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http://www.ema.europa.eu (accessed 15/5/2013)

VIEW Extension Study
2-Year VIEW I Extension
"4 years on aflibercept…"

- N = 323
- Continued "capped PRN" regimen x 2 years (q3 mo monitoring)
- Amended protocol to q2 mo dosing + monitoring
- Average 11 injections over 2 years
- BCVA maintained c/t end of VIEW I
- No new safety signals detected

VIEW Subanalyses
Influence of Anatomic Characteristics on Outcomes

Early Persistent Fluid Analysis

N=1815

18.8% 2q4 vs 29.4% Rq4

VA benefit @ 52w greatest in 2q4 (p<.05)

RPE Elevation Analysis

N=1349

RPE flattening 2q4 59.6% 2q8 52.6% Rq4 45.7% (p<.05)

Aflibercept arms 23-50% more effective in RPE flattening

G Jaffe, ASRS, Toronto 2013
J Kitchens, Retina Subspecialty Day, AAO, New Orleans 2013

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VIEW Subanalyses
Proactive vs Reactive Rx during 2nd year

- Post hoc analyses
- Subgroup of pts lose vision during 2nd year – when Rx reactive
- **50%** of pts did well on q3 months aflibercept
- **20%** of pts lost VA between visits > never came back despite > 5 Rx
- **VA loss not preceded by OCT (CRT) changes**
- "Mostly driven by pts /w PED component"

Proactive Rx
PED component of CNV complex

G Richard, WOC, Tokyo 2014
U Schmidt-Erfurth, COPHY, Lisbon 2014

Athens Vision

«Αποτελεσματικότητα»
Αλλαγή αντι VEGF Παράγοντα

Bevacizumab > Ranibizumab

Ehlers JP et al, 30% 3+ γραμμές ΟΟ ↑

Ranibizumab > Aflibercept

MEEI, n=102, ανατομική ανταπόκριση (IRF, SRF)
διατήρηση ΟΟ στους 4 μήνες παρακολούθησης
+ 2 εβδομάδες μεταξύ θεραπειών

Emory, n=96, ανατομική ανταπόκριση (23% PED)
διατήρηση ΟΟ στους 4 μήνες παρακολούθησης

1. *Ehlers JP et al, Ophthalmic Surg Lasers Imaging 2010;41(2):182-189*
2. *Yonekawa Y et al, Am J Ophthalmol 2013;in press*
3. *Ho VY et al, Am J Ophthalmol 2013; in press*

Athens Vision Case Series
Aflibercept on "Refractory" wAMD Cases

- N = 10
- Pre-Eylea = 32 mo, 17 injections (4-40)
- Post-Eylea > 6 mos f/u
- Persistent exudation (IRF, SRF, PED)

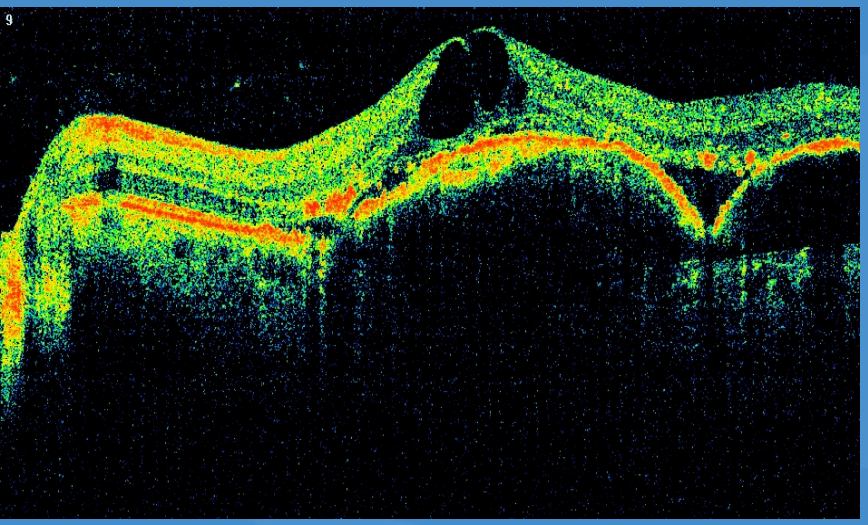
	PRE - EYLEA	POST - EYLEA
BCVA	20/78	20/64 (p=0.33)
CFT	530 (221)	329 (171) (p=0.06)
SRF	140 (86)	19 (34) (p=0.002)
PED	406 (211)	270 (226) (p=0.23)

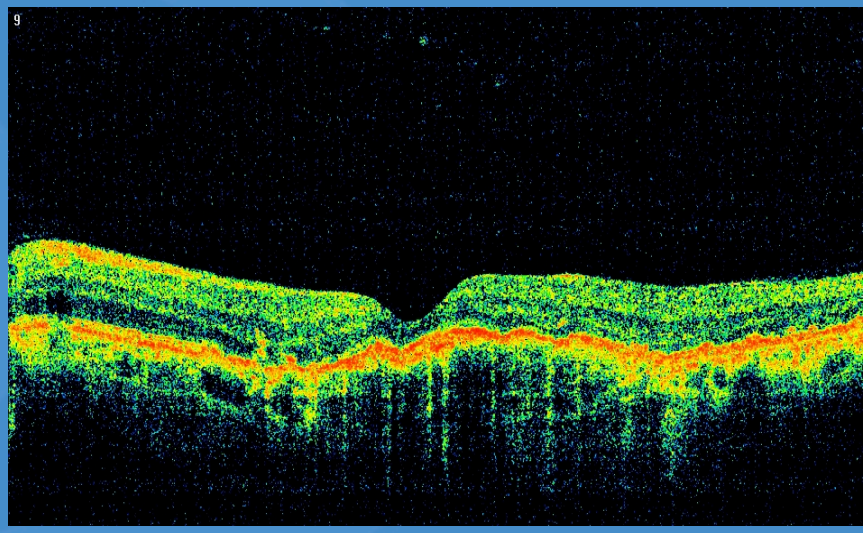
8/10 completely resolved SRF
8/10 reduced PED height
Most exudative features recurred at 6-7 weeks

A Charonis et al, GVRS, 2014

Athens Vision

Case Presentation 1





s/p Avastin x 12 (qmo x3)
BCVA 20/100

s/p Eylea x3 (qmo x3)
BCVA 20/63

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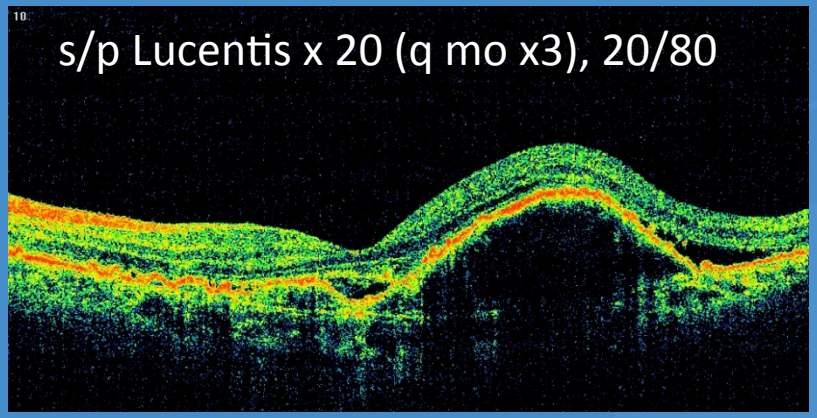
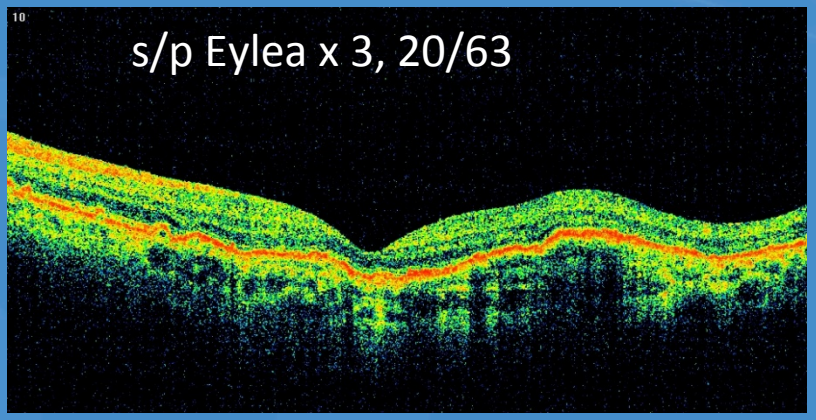
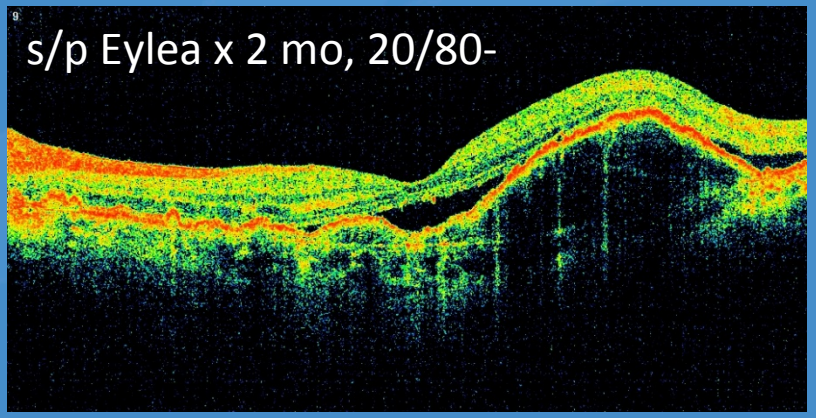
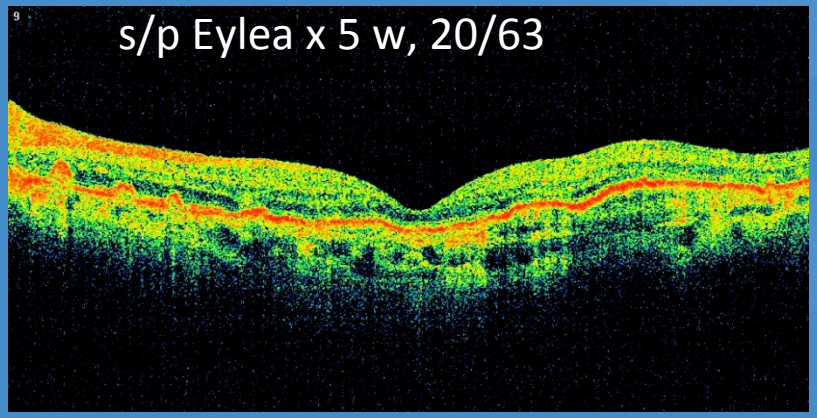
Case Presentation 2









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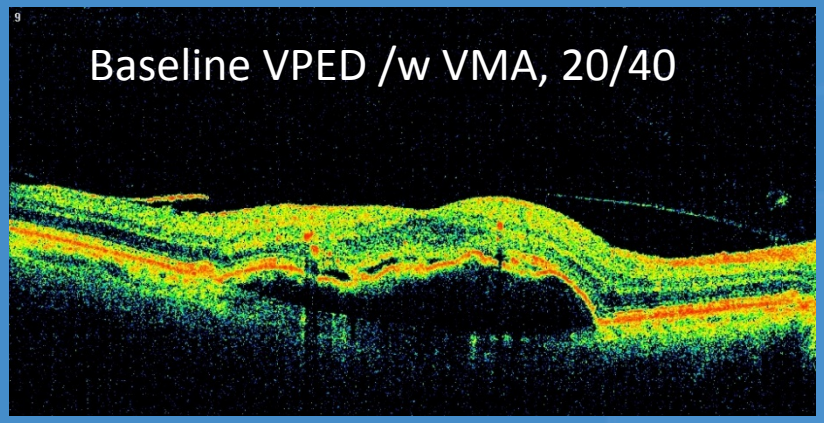
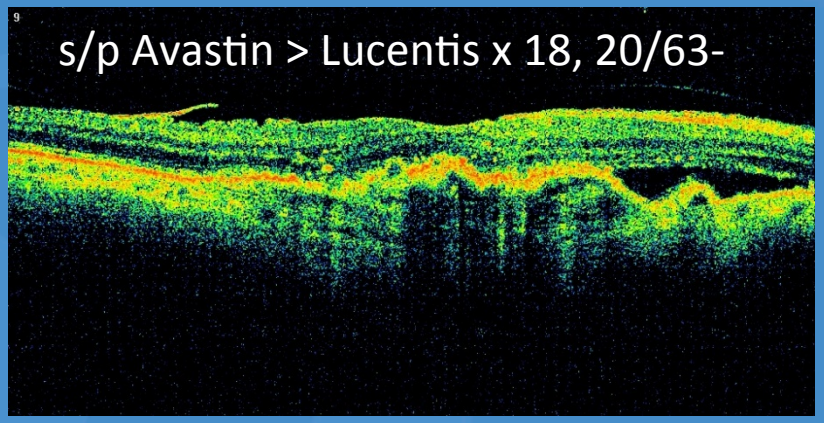
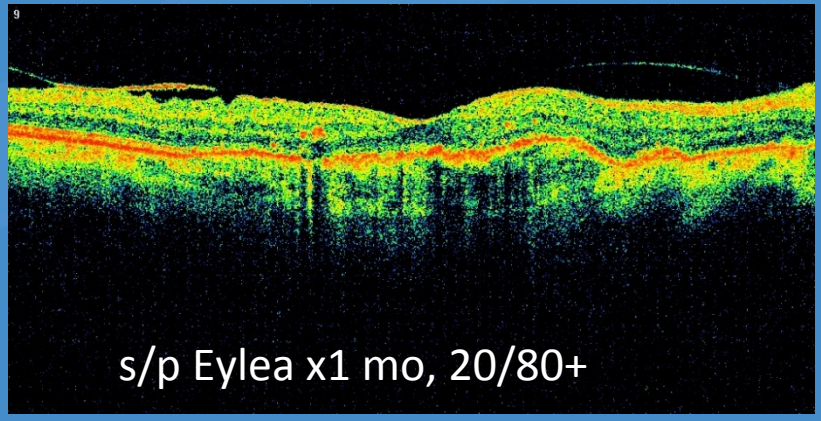
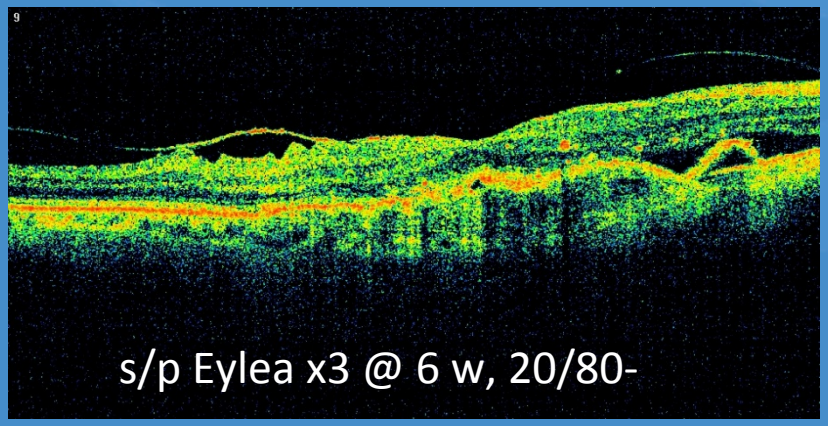
Case Presentation 3









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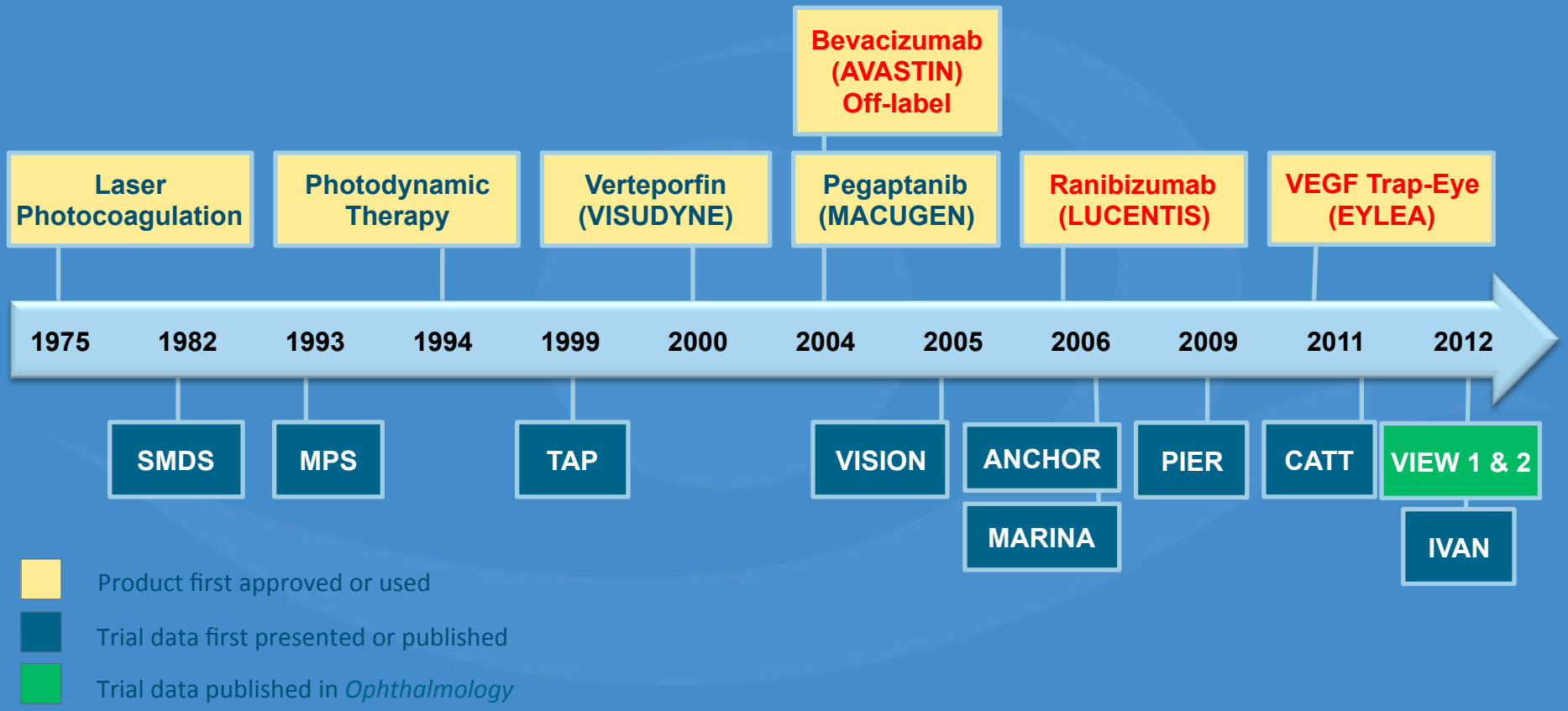
Αποκωδικοποιώντας τα Δεδομένα των Πολυκεντρικών Μελετών...

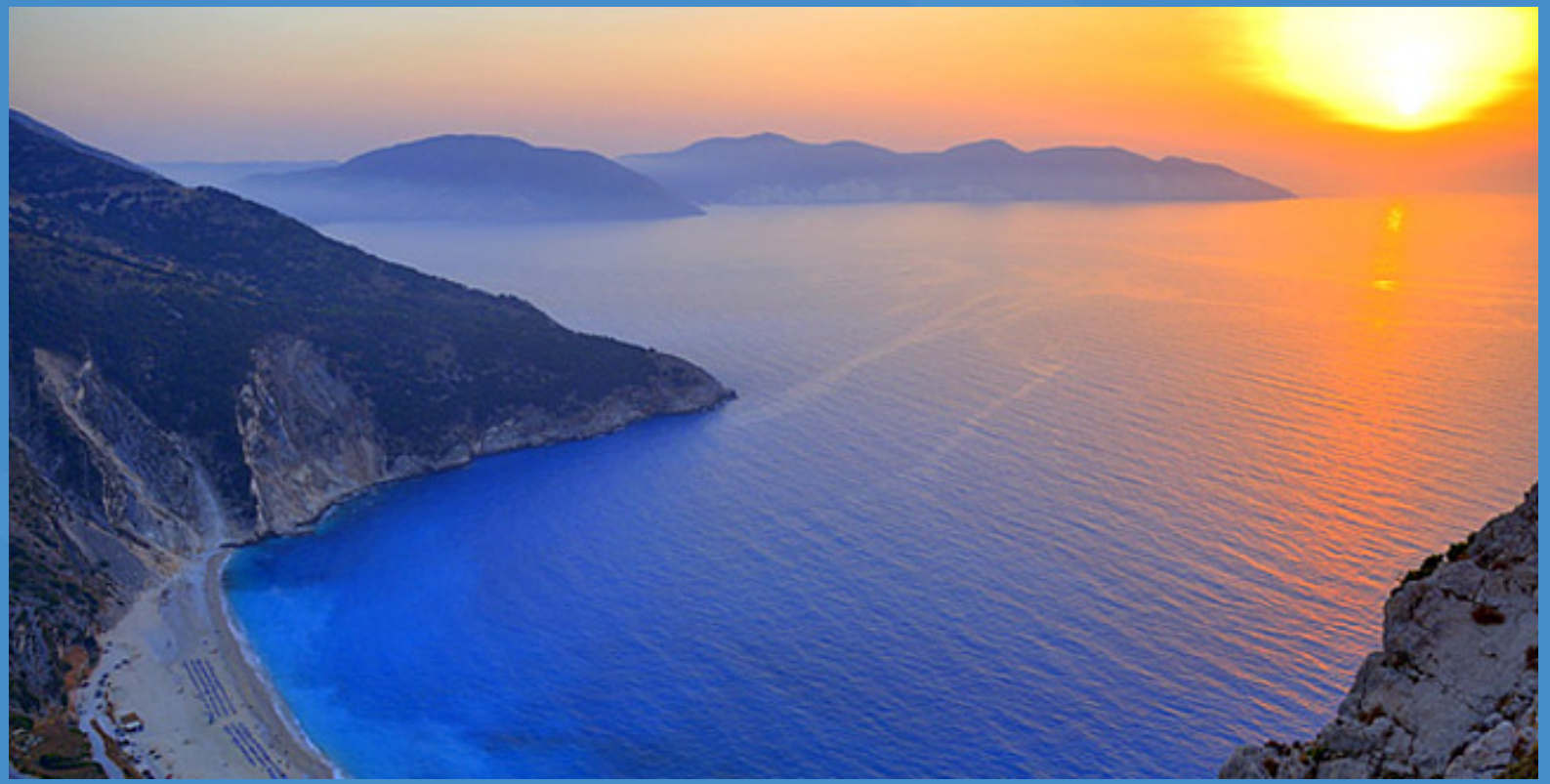
- **Προληπτική (proactive)** vs **Αντιδραστική (reactive) Rx**
- **Εξατομικευμένη (individualized)** vs **Βάσει πρωτοκόλλου Rx**

- **Επιλογή αντι VEGF παράγοντα**
  - **Βιοδείκτες (ανατομία βλάβης, μοριακοί + γενετικοί δείκτες)**
  - **Δυνατότητα εναλλαγής (? ταχυφυλαξία)**
  - **Προσβασιμότητα**
  - **Συμμόρφωση**

wet AMD: Milestones in Treatment



ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; CATT = Comparisons of Age-Related Macular Degeneration Treatments Trials; IVAN = A Randomised Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; MPS = Macular Photocoagulation Study Group; PIER = Phase IIIb, Multi-center, Randomized, Double-Masked, Sham Injection-Controlled Study of Efficacy and Safety of Ranibizumab in Subjects With Subfoveal CNV With or Without Classic CNV Secondary to AMD; SMDS = Senile Macular Degeneration Study; TAP = Treatment of AMD With Photodynamic Therapy; VIEW 1 & 2 = Vascular Endothelial Growth Factor Trap-Eye for Neovascular Age-Related Macular Degeneration; VISION = VEGF Inhibition Study in Ocular Neovascularization.



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