



Incorporating the
Latest Findings From
Clinical Trials Into the
Management of
Diabetic Retinopathy
for the Comprehensive
Ophthalmologist

Diana Do MD
Course #235
Sunday, October 25
2:00 – 3:00 PM
West 3018

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Course Outline:
Diagnosis and Management of Non-Proliferative Diabetic
Retinopathy

David Telander, MD, PhD
UC Davis

- I. Update on glycemic control and retinopathy
 - a. Epidemiology Reminders:
 - i. 18.2 million American have diabetes
 - 1. 5.2 million don't know they have it.
 - ii. Type 2 diabetes accounts for up to 95% of all diabetes
 - 1. 8% of the population aged 20 and older.
 - 2. 18.6% of the population 60 years and older
 - 3. The prevalence of type 2 diabetes has tripled in the last 30 years, much of it due to an increase in obesity
 - 4. Only 50% of patients with diabetes receive regular dilated eye examinations, and many patients go blind without treatment
 - iii. WESRC
 - 1. Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) -- valuable prevalence and risk factors information.
 - 2. In the younger-onset group (diagnosis of diabetes < 30 yrs and taking insulin -- presumably type 1), retinopathy, either proliferative or non-proliferative, was seen in 13% of patients with less than a 5-year duration of diabetes and in 90-98% of patients with a duration of 10 to 15 years. Type 2 group (older onset) was 29% at 5 years and 78% at 15 years.
 - 3.
 - b. Glycemic control and retinopathy?
 - i. Glycemic fluctuations vs. HgbA1C
 - ii. DCCT: Key Facts (Reminders):
 - 1. Showed 3-year risk of developing retinopathy was reduced by 75% in the intensive insulin treatment group compared with the standard treatment group
 - 2. With existing retinopathy -- 50% reduction in the rate of progression of retinopathy compared with controls
 - 3. When stratified by hemoglobin A1C (HbA1C) levels, there was a 35% to 40% reduction in the risk of retinopathy progression for every 10% decrease in HbA1C (e.g., from 8% to 7.2%).
 - iii. UKPDS – similar data for type 2 DM
 - iv. Recommended Goal by the ADA to have HbA1C level below 7%
 - c. What is the Role of Genetics in determining a patient's susceptibility to nonproliferative diabetic retinopathy?
 - 1. Epidemiology Studies:

2. Genetic Polymorphisms: identifying specific markers will refine our screening algorithms and interventions in patients such as high risk patients

Promising Genetic Markers Associated with Any Diabetic Retinopathy (i.e. Risk Markers)

Genetic Marker	Polymorphism	Reference
VEGF genotype	-634CC	Awata ²⁶
Aldose Reductase promoter	(CA) _n repeat; Z-2/X where X is any allele other than Z+2	Demaine ³⁵
IGF-1 promoter	(CA) _n : Heterozygosity for the 192- or 194 base pair alleles	Rietveld ²⁴
SDH promoter	G-888C	Szaflik, J.P.
eNOS promoter	haplotypes 112 (Glu298/4b/-786C) and 222 (Asp298/4a/-786C)	Ezzidi, I

*=at position 634 relative to the transcription start of the VEGF gene, C is present on both alleles

ii. Update on influence of other co-morbidities

1. Hypertension

- a. UKPDS: Tight blood pressure control resulted in a 37% reduction in microvascular diseases, predominantly reduced risk of retinal photocoagulation, when compared to less tight control
- b. Promise in the renin-angiotension aldosterone system inhibitors – inhibitors in this pathway to decrease BP effective in limiting retinopathy

2. Hyperlipidemia

- a. WESDR, a population-based study, and the ETDRS found that elevated levels of serum cholesterol were associated with increased severity of retinal hard exudates
- b. Elevated serum triglyceride levels were also associated with a greater risk of developing high-risk PDR in the ETDRS patients

3. Renal Disease: proteinuria and increased BUN is a predictor of retinopathy

4. Pregnancy: q 3 month screening.

iii. Screening Schedules:

Eye examination schedule		
Time of onset of diabetes mellitus	Recommended time for first examination	Routine minimum follow-up
Less than 30 years of age	5 years after onset	Annually
Age 30 and older	At time of diagnosis	Annually
Before pregnancy	Before or soon after conception	At least every 3 months

Recommended follow-up schedule	
Status of retinopathy	Follow-up (months)
No retinopathy or microaneurysms only	12
Mild/moderate NPDR without macular edema	6 to 12
Mild/moderate NPDR with macular edema that is not clinically significant	4 to 6
Mild/moderate NPDR with clinically significant macular edema	3 to 4
Severe/very severe NPDR	3 to 4

1. In UK, out of 15,080 pt with DM only 479 (3%) were referred to ophthalmologist and 80% of these had DR.
 2. Tele-imaging – Many advances and many advantages
- II. Recognizing severe non-proliferative diabetic retinopathy and its importance
- a. Reminders: Classification
 - i. Mild nonproliferative diabetic retinopathy
 1. Microaneurysms only
 - ii. Moderate nonproliferative diabetic retinopathy
 1. More than just microaneurysms but less than severe nonproliferative diabetic retinopathy
 - iii. Severe nonproliferative diabetic retinopathy
 1. Any of the following:
 - a. More than 20 intraretinal hemorrhages in each of four quadrants
 - b. Definite venous beading in more than two quadrants
 - c. Prominent intraretinal microvascular abnormalities in more than one quadrant and no signs of proliferative retinopathy
- III. Management of severe non-proliferative diabetic retinopathy
- a. Early PRP laser or observation: Diabetic Retinopathy Study (DRS)
 - b. Analyses of ETDRS data have suggested that early scatter treatment is particularly effective in reducing severe visual loss in patients with type 2 diabetes. These data provide an additional reason to recommend early scatter photocoagulation in older patients with very severe NPDR.

QuickTime™ and a
decompressor
are needed to see this picture.

- c.
- d. Diabetic Macular Edema: see following sections
- e. Macular Ischemia
- f. Medical Management for severe NPDR
 - i. Aspirin
 - ii. protein kinase C (PKC) β inhibitor – ruboxistaurin—
 - 1. Though successful in animal studies and smaller clinical studies, the drug showed only marginal success in initial clinical trials
 - 2. More recent data continues to show benefit
 - iii. Advanced Glycosylation End Product Inhibitors
 - iv. Statins
 - v. Antioxidants
 - vi. Anti-VEGF
 - vii. renin-angiotensin blockade
 - 1. DIRECT study using oral candesartan 32 mg daily

References:

Abhary S, Hewitt A, Burdon K, Craig J. A systematic meta-analysis of genetic association studies for diabetic retinopathy. Diabetes. 2009 Jul 8. [Epub ahead of print]

Chew EY, Klein ML, Ferris FL III et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Arch Ophthalmol 1996; 114:1079-1084

Ferris F. Early photocoagulation in patients with either type I or type II diabetes. Trans Am Ophthalmol Soc 1996; 94:505-537

Jyothi S, Elahi B, Srivastava A, Poole M, Nagi D, Sivaprasad S. Compliance with the quality standards of National Diabetic Retinopathy Screening Committee. Prim Care Diabetes. 2009 May;3(2):67-72. Epub 2009 Jun 18.

Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol. 2007 Jul-Aug;14(4):179-83. Review.

Klein BEK, Moss SE, Klein R et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudates. Ophthalmology 1991; 98:1261-1265.

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Centers for Disease Control (www.cdc.gov/diabetes/news/docs/dpp.htm)

McGill JB Improving microvascular outcomes in patients with diabetes through management of hypertension.. Postgrad Med. 2009 Mar;121(2):89-101. Review.

Moss S, Klein R, Klein B. Factors associated with having eye examinations in persons with diabetes. Arch Fam Med 1995; 4:529-534

Wright AD, Dodson PM. Diabetic retinopathy and blockade of the renin-angiotensin system: new data from the DIRECT study programme. Eye. 2009 Jul 24.

2009 Meeting of the American Academy of Ophthalmology

Anti-VEGF Therapies for Diabetic Macular Edema



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Financial Disclosure

Johns Hopkins University, the employer of Dr. Nguyen, has received research funding from the National Eye Institute, Genentech, and Regeneron.

Dr. Nguyen receives the Physician Scientist Award from the Research to Prevent Blindness Foundation.

This presentation will discuss the off-label use of ranibizumab and VEGF Trap Eye for diabetic macular edema.

READ 2 Study: **Ranibizumab for Edema of the mAcula in Diabetes**

Preliminary One Year Updates

Quan Dong Nguyen, MD, MSc, Jeffrey S. Heier, MD, Syed
Mahmood Shah, MB BS, Diana V. Do, MD, Jennifer Lim, MD,
David Boyer, MD, Prema Abraham, MD, Pravin Dugel, MD, and
Peter Campochiaro, MD
for
the READ-2 Research Group

**The READ-2 Study is sponsored by the
Juvenile Diabetes Research Foundation**

**The study drug, ranibizumab, is
provided by Genentech, Inc.**



READ-2

Ranibizumab for Edema of the
mAcula in Diabetes



The READ 2 Research Group

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Jeffrey Heier, MD
Jennifer Lim, MD
Quan Dong Nguyen, MD, MSc

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David Wilson, MD

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Jonathan Pollack, MD
Alan Thach, MD

READ-2

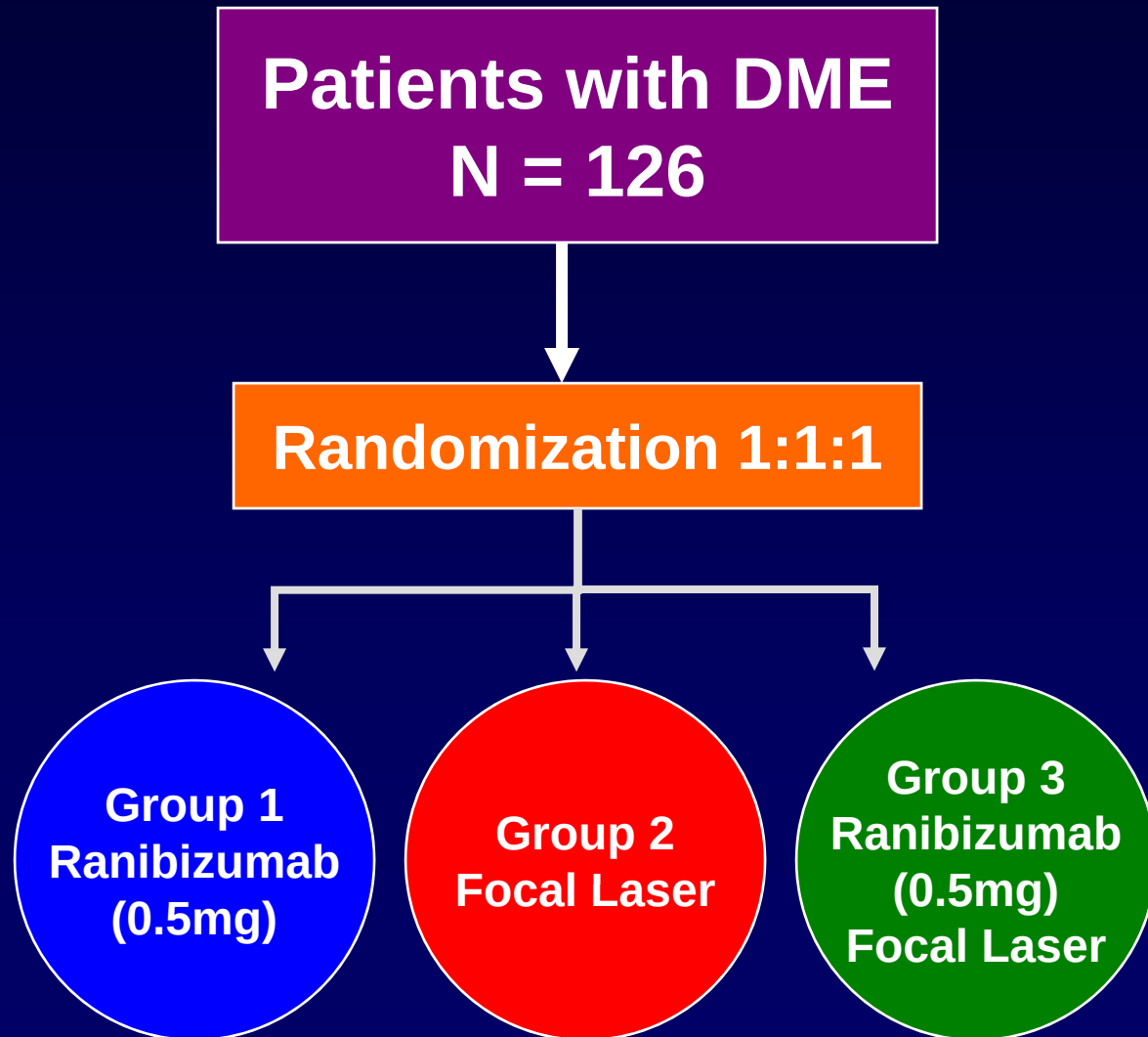
Study Design and Objectives

- Evaluate the effects of intravitreal ranibizumab (0.5 mg) compared to
 - Focal laser
 - Combination of ranibizumab + focal laser
 - Subjects with DME

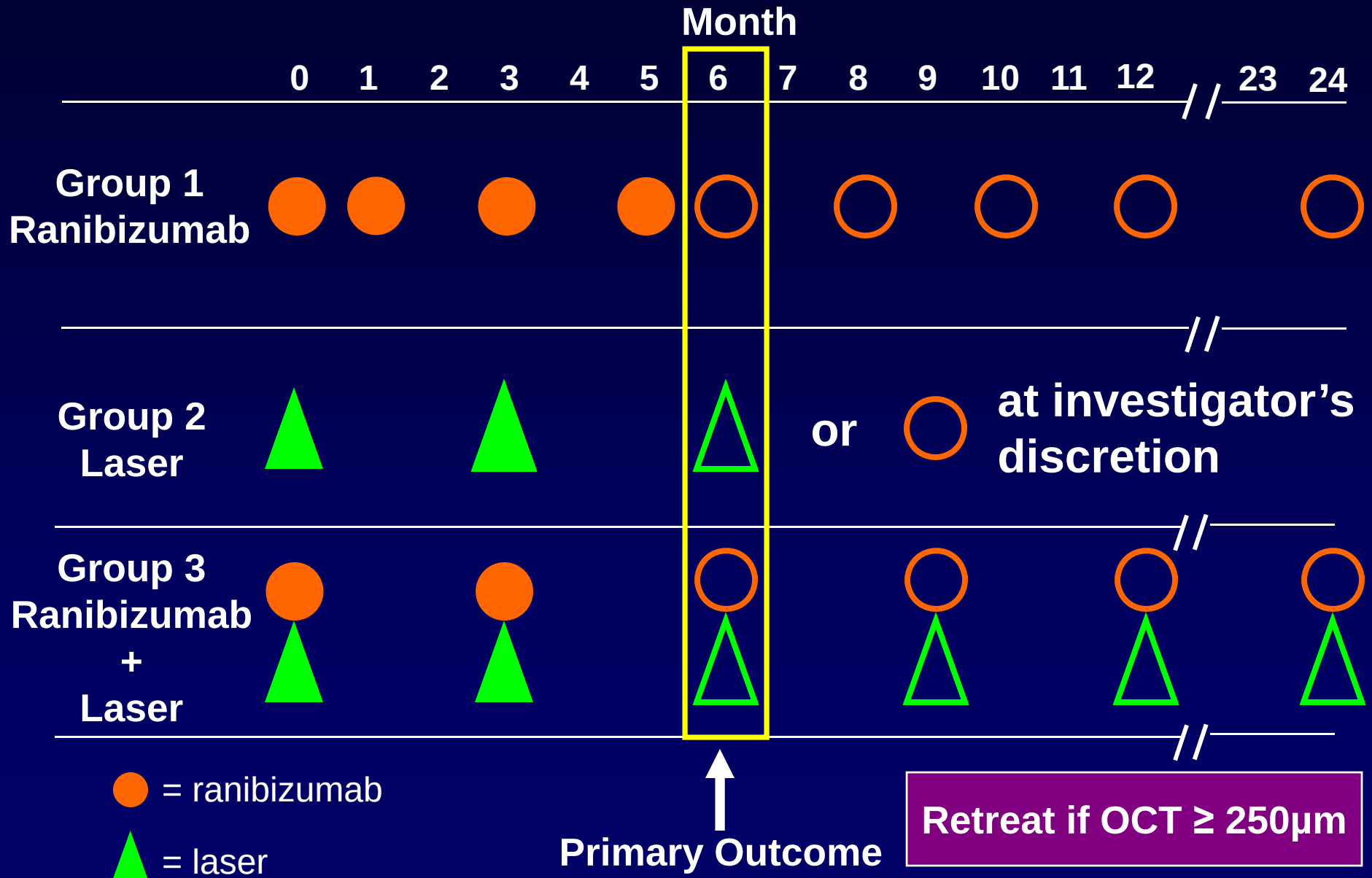
Key Eligibility Criteria

- Age ≥ 18 years
- BCVA (Snellen equivalent) 20/40 to 20/320
- DME with retinal thickness ≥ 250 μm on OCT
- Prior treatment allowed if:
 - Focal laser ≥ 3 months
 - Intraocular steroids ≥ 3 months
 - Panretinal photocoagulation ≥ 3 months
 - Vitrectomy surgery ≥ 3 months
 - Anti-angiogenic agents ≥ 2 months

Study Design



READ 2 Treatment Design



Baseline Characteristics

	Group 1 Ranibizumab (n=42)	Group 2 Laser (n=42)	Group 3 Ranibizumab + Laser (n=42)
Gender (% women)	30.9%	45.2%	47.6%
Race (% white)	76.2%	64.3%	69.1%
Age (mean years)	62.5	62.1	62.1
Mean VA (letters read)	24.3	27.7	25.1
Mean VA (~Snellen equivalent)	20/80	20/80 ⁺²	20/80
Mean Excess Foveal Thickness (µm)	204.2	224.1	256.6
Hemoglobin A1C	7.39	7.58	7.76

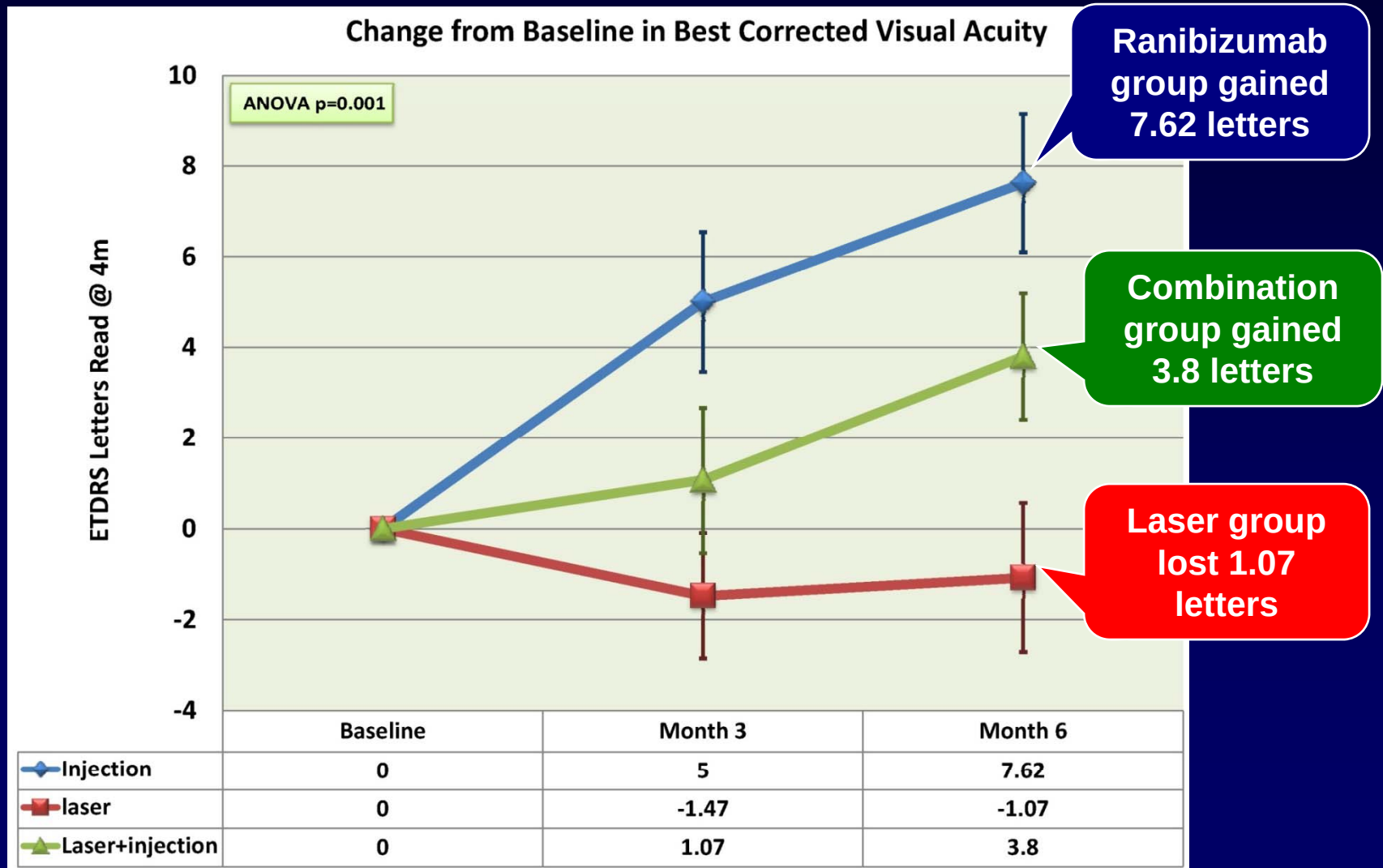
READ-2 Updates at Month 12

- Analyses were performed on 115 patients for the 6-month results
- 112 of 126 participants have remained in the Study at month 12
 - 10 patients have discontinued from the study
 - 4 patients missed month 12 visits
 - Analysis being done, including LOCF, for 116 subjects
- Preliminary data analyses of the 12-month results are being presented

Visual Acuity and OCT Results

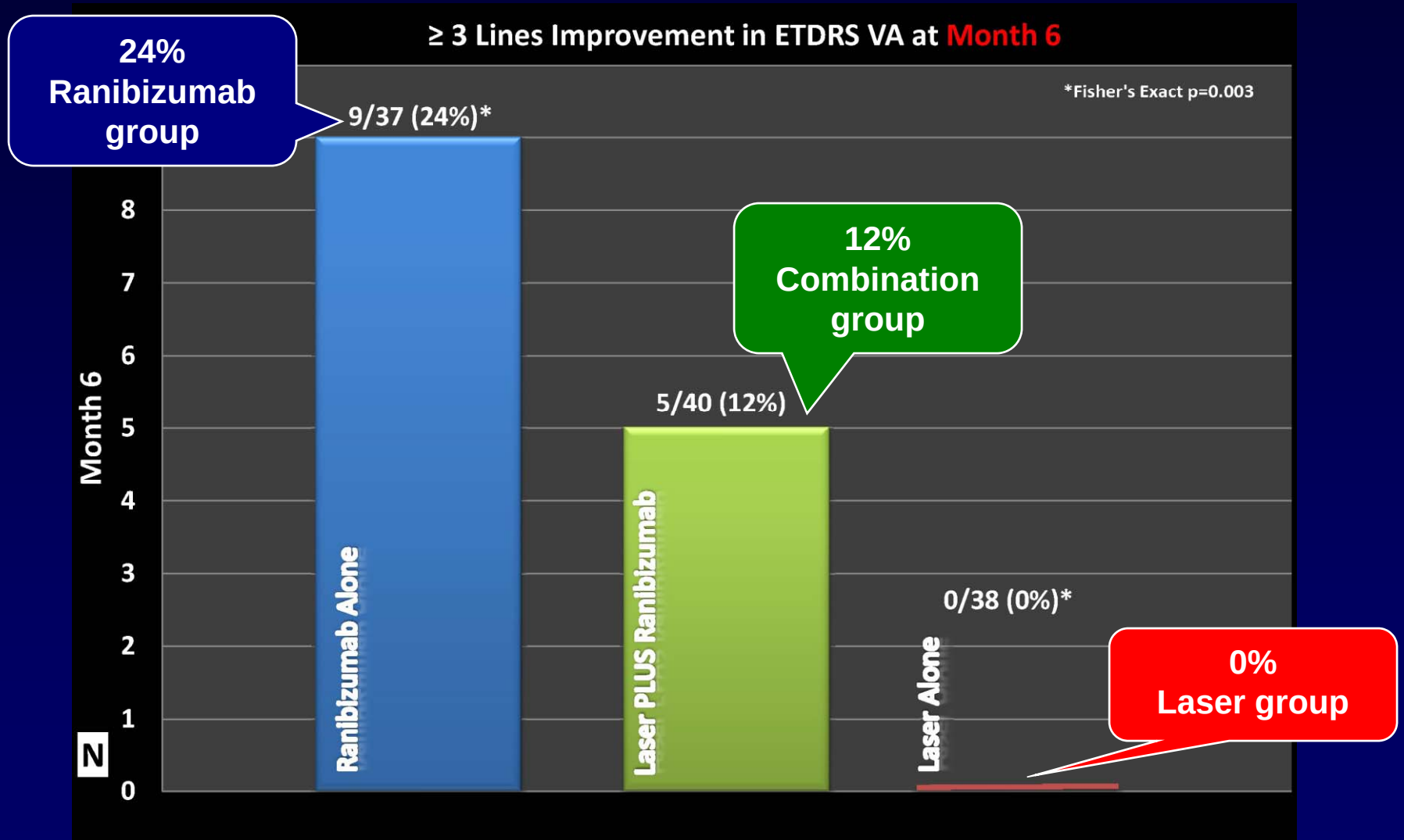
Month 6

Change in Visual Acuity from Baseline



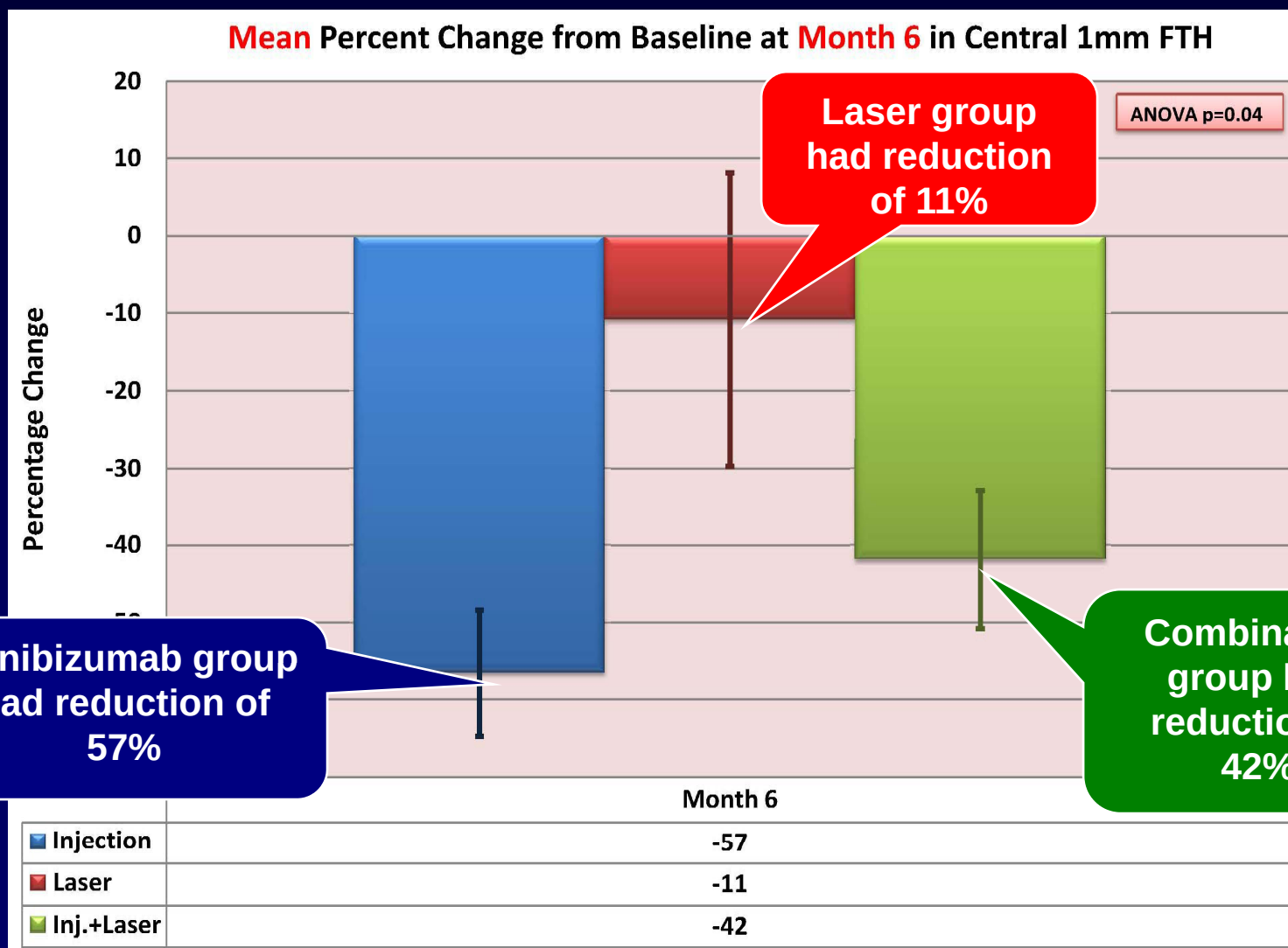
Month 6

Improvement in Visual Acuity (≥ 3 Lines)



Month 6

Mean Change in Excess Retinal Thickness



Month 12

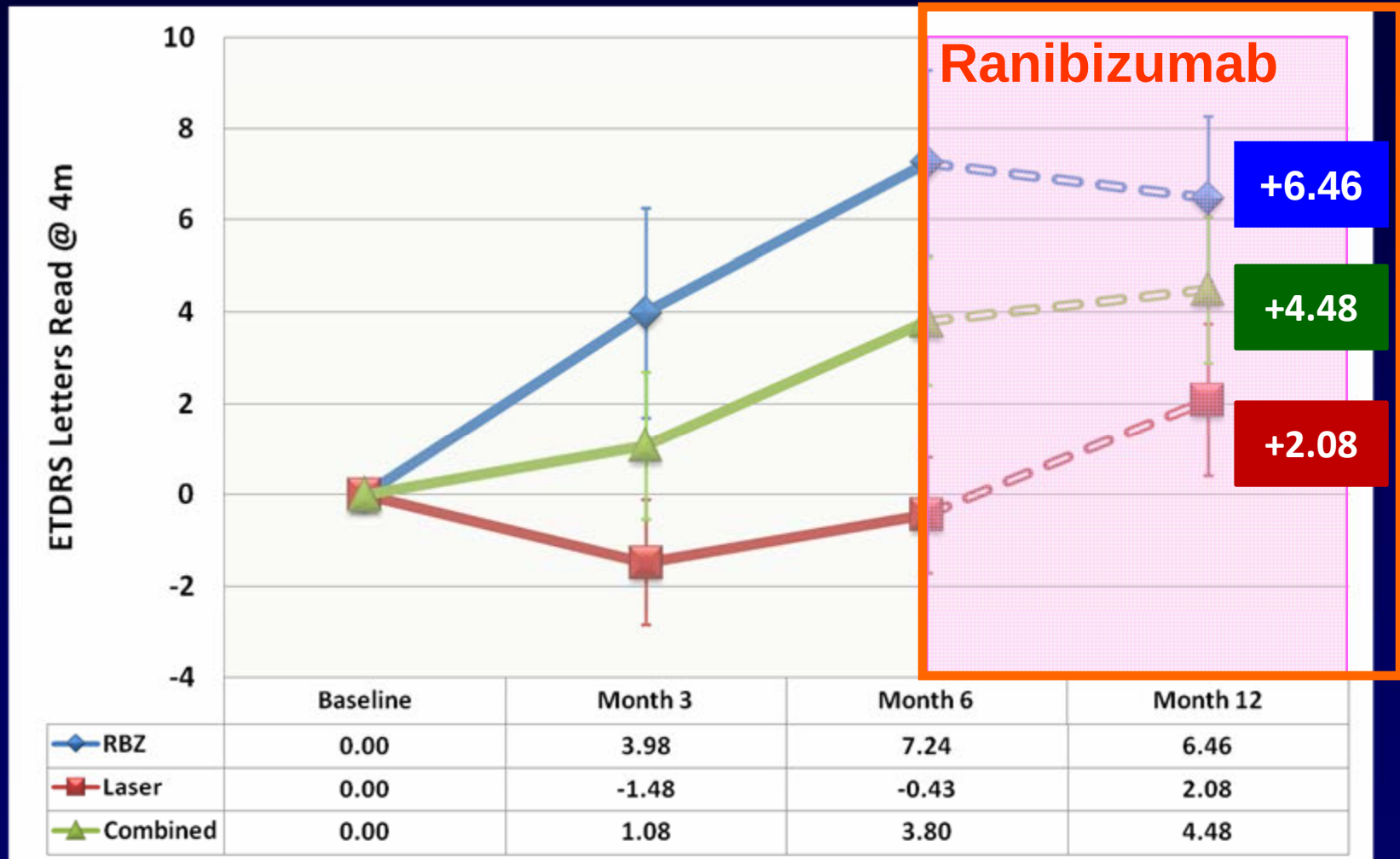
Visual Acuity and

OCT Results

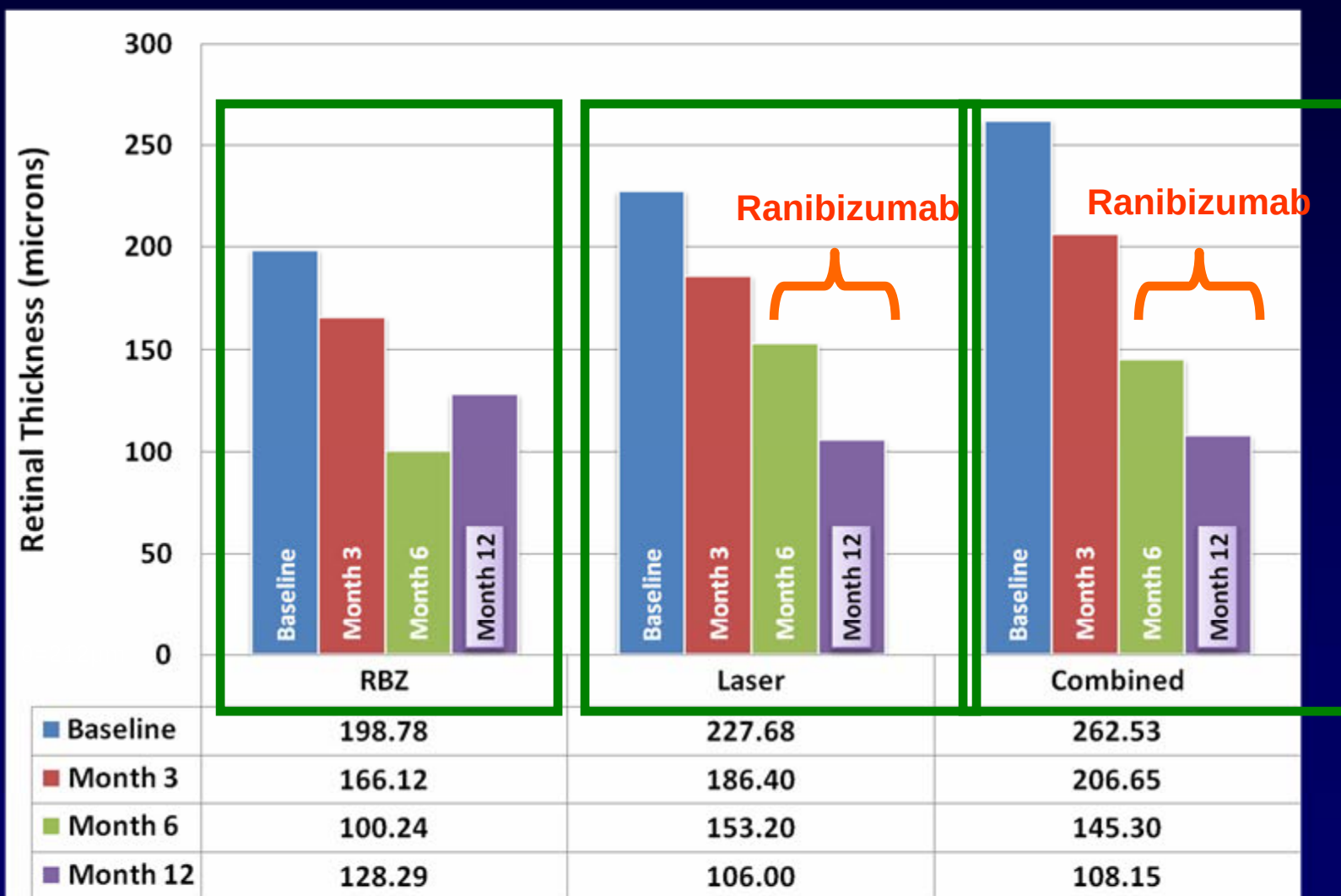
Month 12 Results: Distribution of Treatment Subtype among Three Groups

Group 1	M6	M8	M10
Laser Only	0	0	0
Injection Only	22	28	21
Total Treated	22/37	28/38	21/33
Group 2	M6	M8	M10
Laser Only	3	0	0
Injection Only	24	23	22
Combined	0	0	0
Total Treated	27/38	23/36	22/36
Group 3	M6	M9	
Laser Only	2	0	
Injection Only	18	14	
Combined	8	6	
Total Treated	28/40	20/36	

Month 12: Mean Change in Visual Acuity from Baseline



Month-12: Excess Central Foveal Thickness



Safety Results

Safety

- Study conduct monitored by the DSMC
- No drug/laser-related serious ocular adverse events
- No drug/laser-related serious systemic adverse events

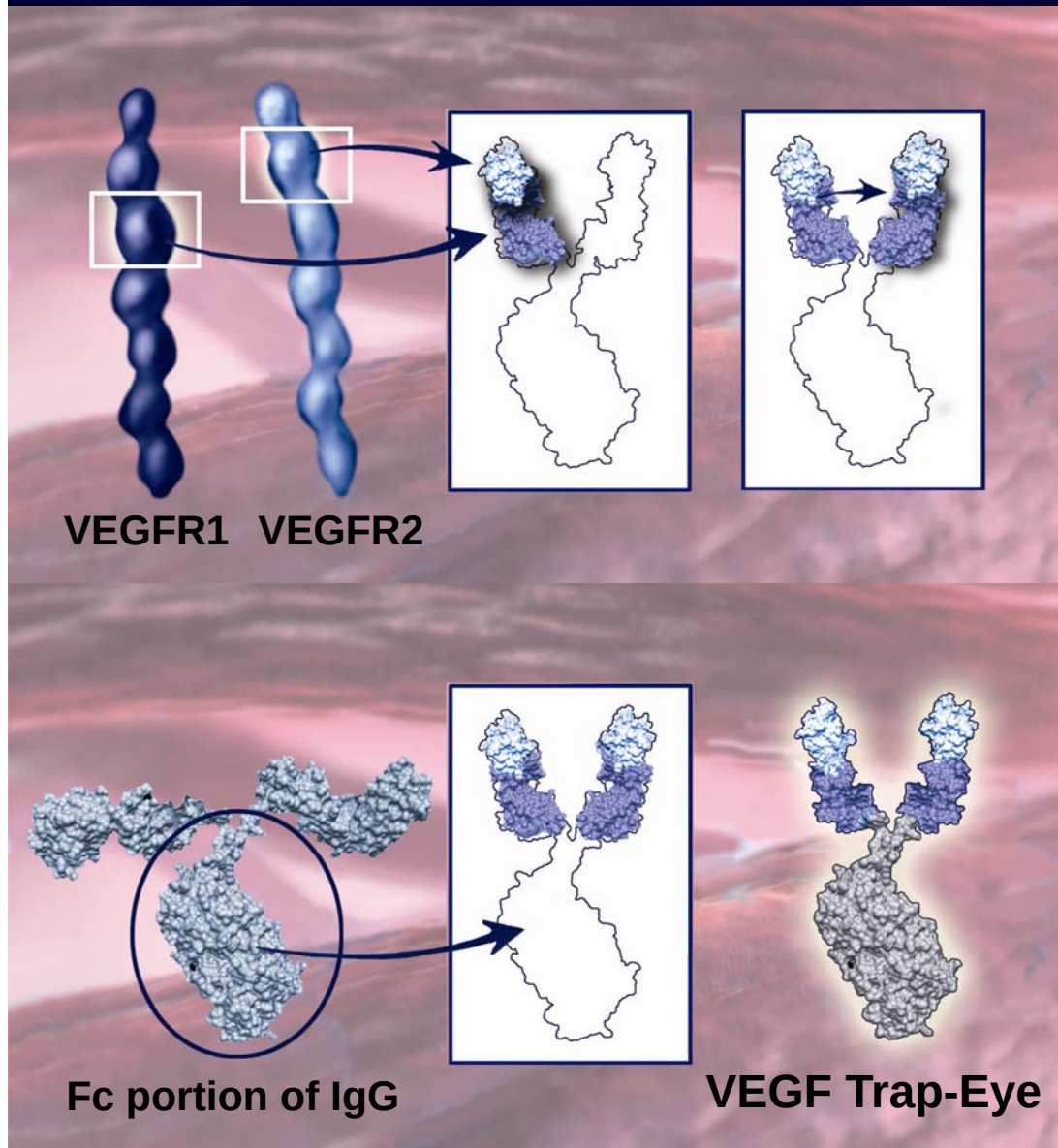
Summary

- Treatment of DME for 6 months with ranibizumab produces greater gain in visual acuity and a greater reduction of excess retinal thickening compared to
 - Laser photocoagulation
 - Combination of ranibizumab plus laser
- During months 6-12, patients in the laser and combination groups were switched to ranibizumab
- Patients who were randomized to ranibizumab during the first 6 months showed no additional improvement between months 6 and 12 in visual acuity or excess retinal thickness
 - More frequent treatments with ranibizumab may be necessary to enhance benefits
- Long term follow-up is necessary to determine if benefits from ranibizumab are sustained

VEGF Trap-Eye for DME

VEGF Trap-Eye

Specifically Designed to Block VEGF



Fusion protein of key domains from human VEGF receptors 1 and 2 with human IgG Fc

Blocks all VEGF-A isoforms and placental growth factor (**PlGF**)

High affinity - binds VEGF-A and PlGF more tightly than native receptors

Contains **all human** amino acid sequences

Penetrates all layers of the retina (MW ~110,000)

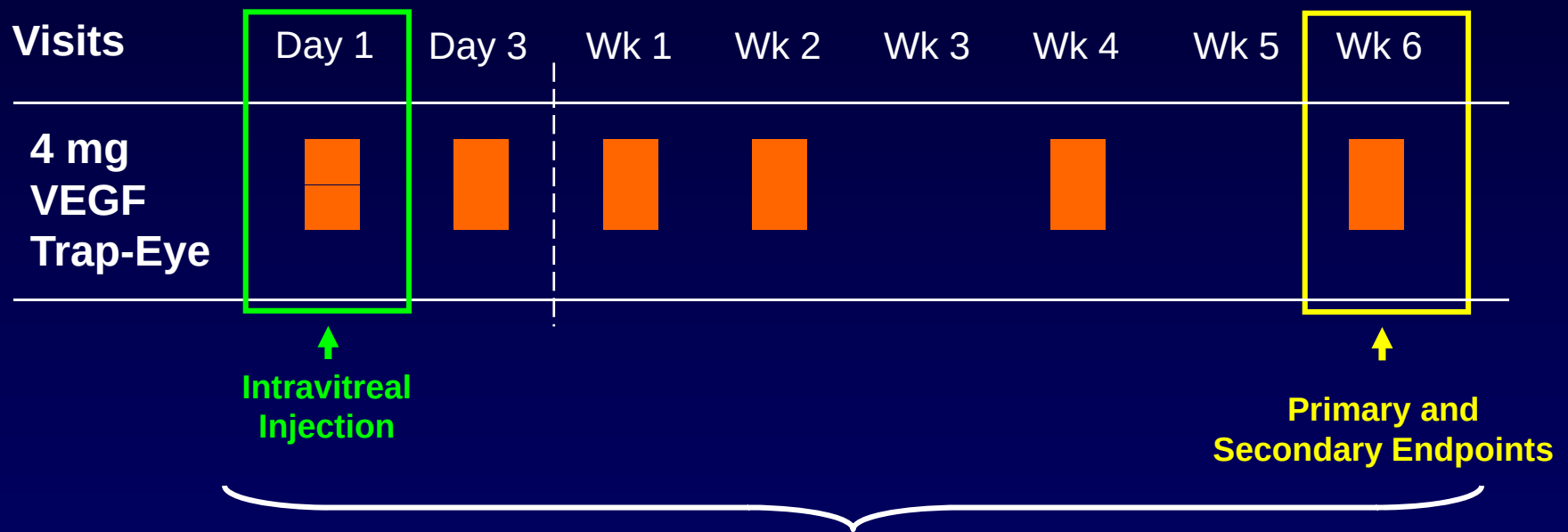
VEGF Trap-Eye is **specially purified and formulated** for intravitreal injection

IgG=immunoglobulin G; MW=molecular weight

VEGF Trap-Eye DME Phase 1: Study Design

- Open label, 5 patients
- Single intravitreal injection of 4 mg VEGF Trap-Eye
- Patients followed for 6 weeks for safety, BCVA, centerpoint retinal thickness on OCT
- Key eligibility criteria
 - BCVA score of 73 to 24 letters (20/40 to 20/320)
 - DME with retinal thickness at the center point ≥ 250 microns
 - Prior treatment allowed:
 - Focal/grid macular photocoagulation, peribulbar corticosteroids, or any other non-intraocular treatment of DME > 4 months
 - Intraocular steroid or anti-VEGF treatment > 6 months
 - Panretinal scatter photocoagulation (PRP) > 4 months

VEGF Trap-Eye DME Phase 1: Study Schedule



Patient assessment at each visit:

- Safety
- BCVA
- Centerpoint retinal thickness
- Macular volume by OCT

VEGF Trap-Eye DME Phase 1: Baseline Characteristics

	Median	Range
Age (years)	65.7	56-75
Gender (M:F)	2:3	
Duration of Diabetes (years)	25.8	20-41
IDDM/NIDDM	4:1	
Patients with Prior Treatments	4*	
Disease Status		
OCT Excess Retinal Thickness	108	88-424
Macular Volume	8.0	2.6-11.6
Median BCVA (Snellen equivalent)	20/50 +1	

*Focal Laser (3); IVK (1); PRP, IVK (1)

IDDM/NIDDM=insulin-dependent diabetes mellitus/non-insulin dependent diabetes mellitus;

IVK=intravitreal Kenalog [triamcinolone acetate]

Do DV et al. In press , BJO 2008

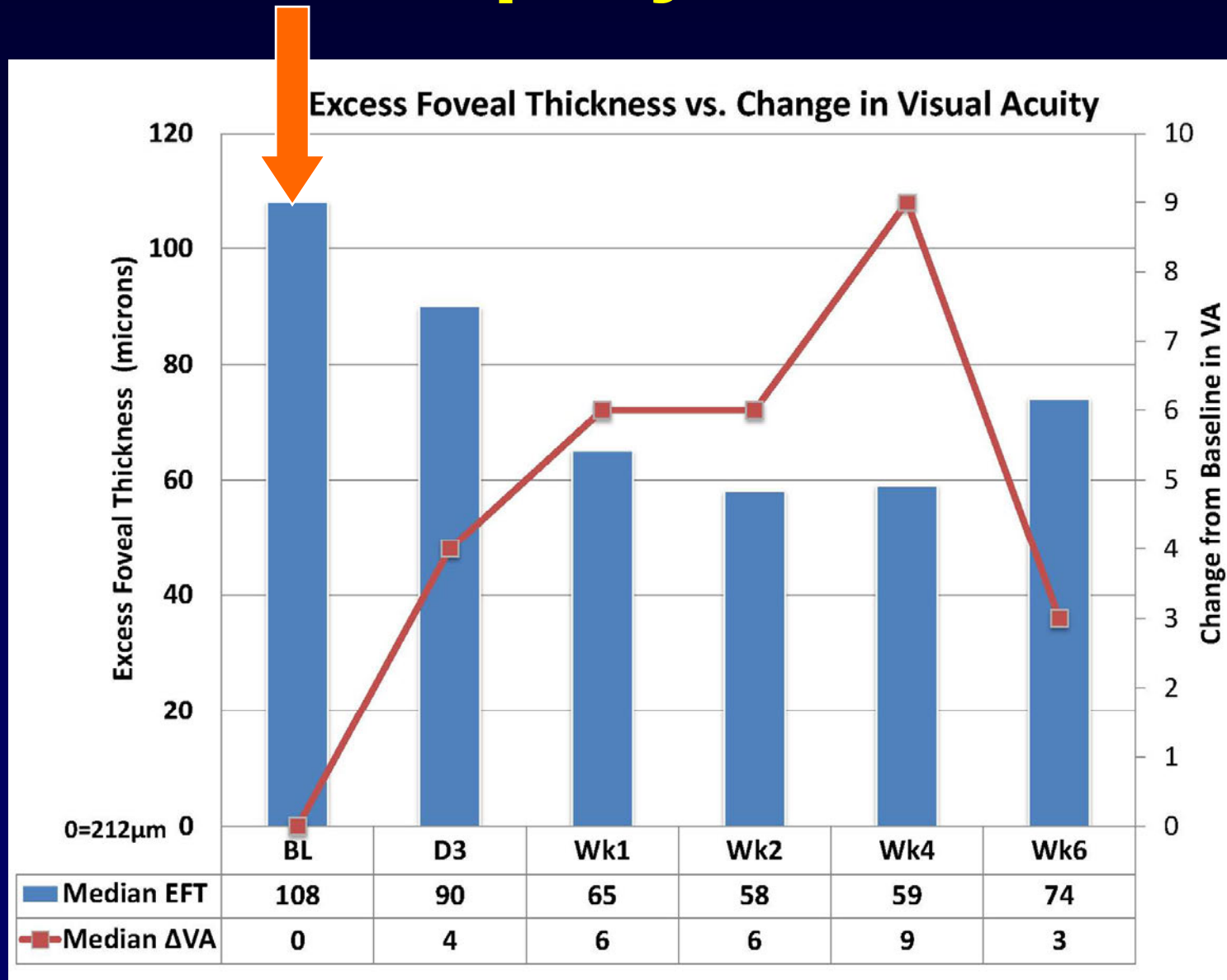
Results of Phase 1 VEGF Trap-Eye for DME

VEGF Trap-Eye DME Phase 1

Safety Results

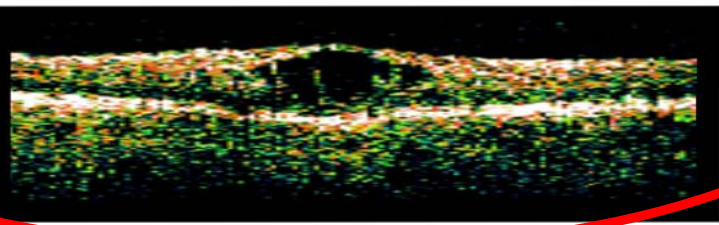
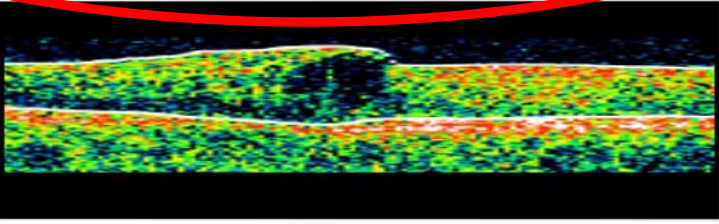
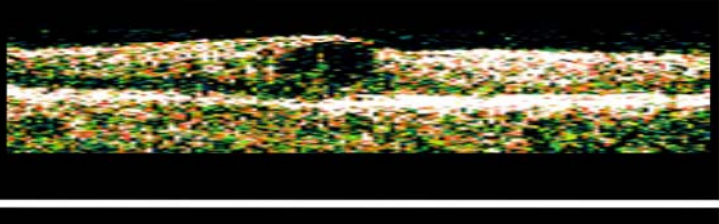
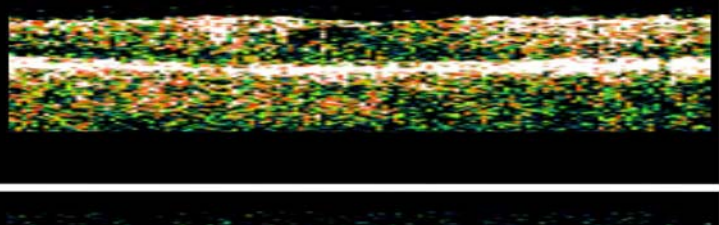
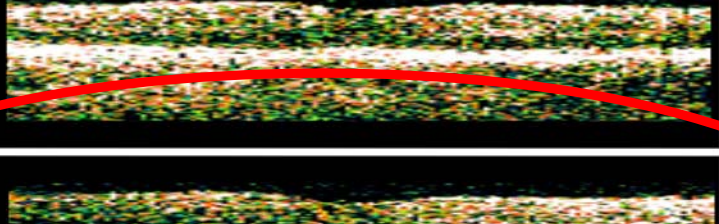
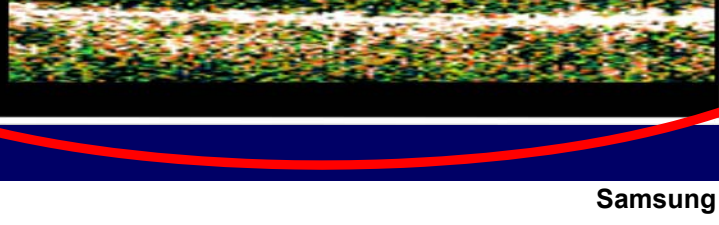
- All ocular adverse events were mild and related to the injection procedure
- No serious ocular or systemic adverse events were reported

VEGF Trap-Eye for DME

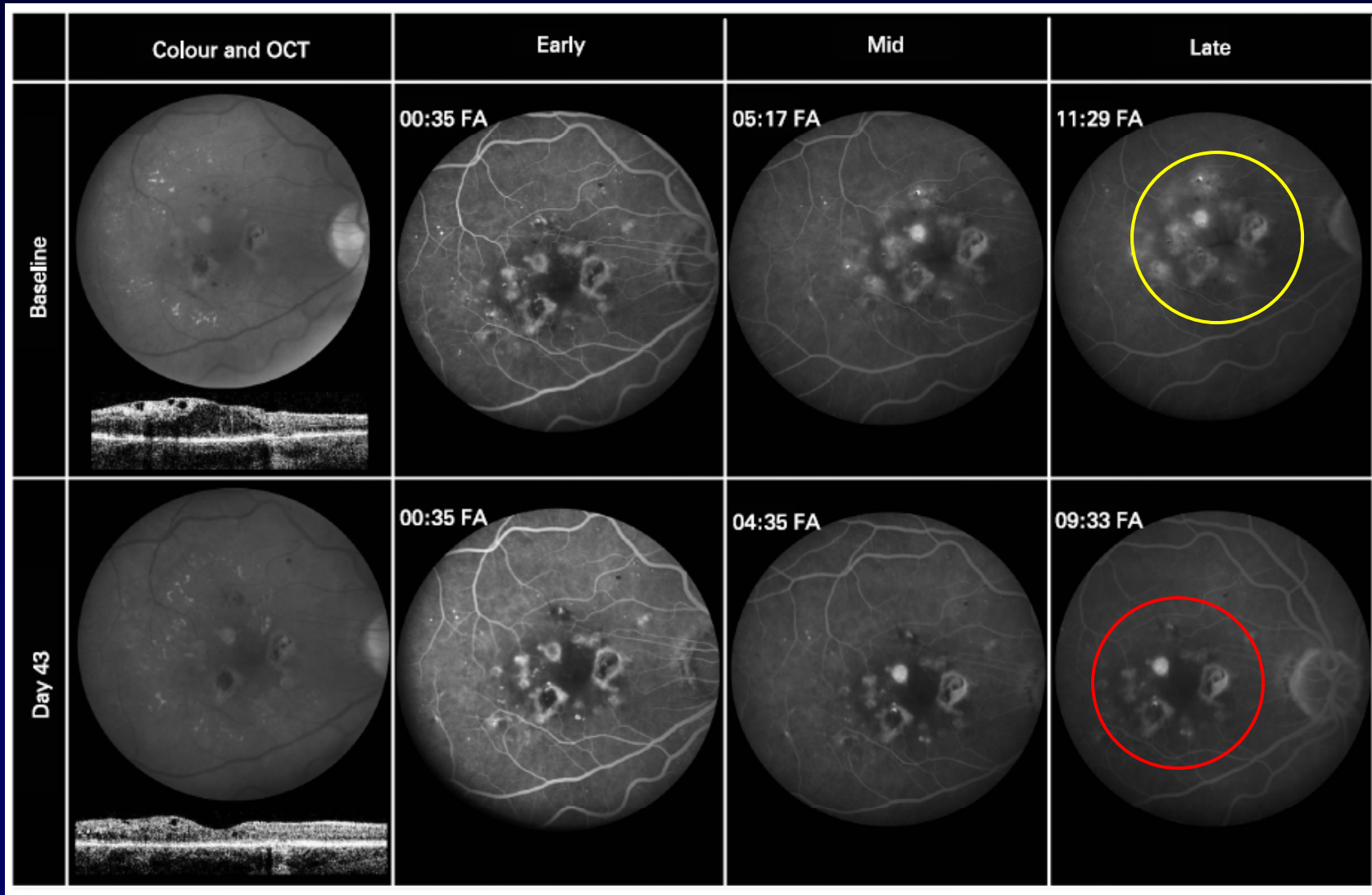


**Intravitreal
VEGF Trap
4mg**



BL	
D3	
Wk1	
Wk2	
Wk4	
Wk6	

VEGF Trap-Eye for DME

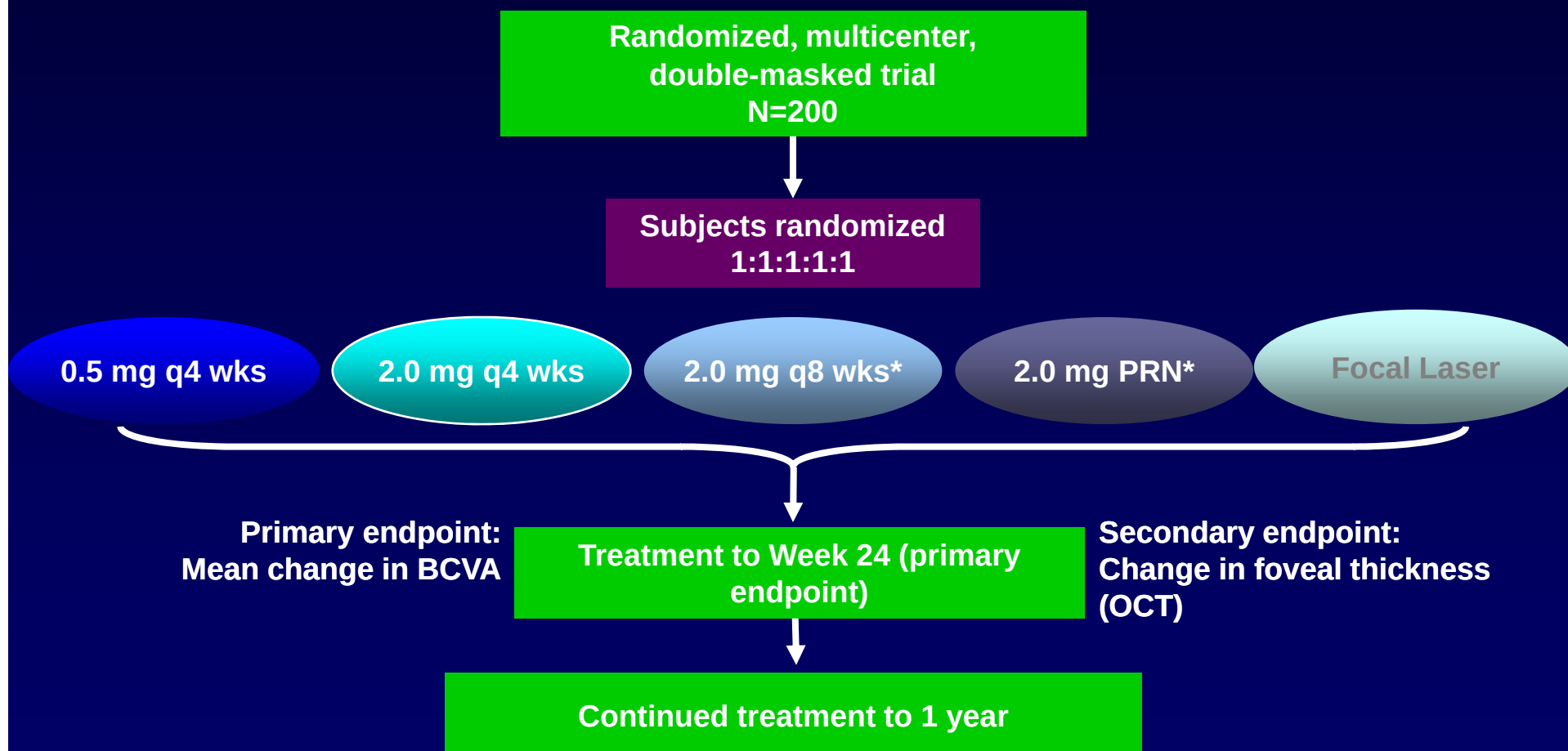


VEGF Trap-Eye

DME Phase 1 Summary

- Open-label, short term, safety study of intravitreal VEGF Trap-Eye in eyes with DME
- Single injection of 4 mg of VEGF Trap-Eye was well tolerated
- VEGF Trap-Eye demonstrated bioactivity in DME:
 - Decreases retinal thickness
 - Improvement in visual acuity
- Phase 2 clinical study underway

VEGF Trap-Eye DME Phase 2 Study Design



*Following 3 monthly loading doses

Conclusion

Potential Treatments for DME with Anti-Angiogenic Approach

- **Ranibizumab** has demonstrated bioactivity and safety through one year of follow up in the READ 2 study
- Phase 3 studies of ranibizumab underway
- **VEGF Trap-Eye** has demonstrated short-term bioactivity and safety in phase 1 studies
- Phase 2 studies underway
- Other therapeutic agents with anti-angiogenic activities in clinical trials
 - Sirolimus
 - PF-04522655 (siRNA)
- Combination therapies

Update on Laser for Diabetic Macular Edema

Diana V. Do, MD

Assistant Professor of Ophthalmology

The Wilmer Eye Institute, The Johns Hopkins University

ETDRS Laser:

- Reduced risk of at least moderate visual acuity loss (most cases enrolled had mild or moderate non-proliferative DR)
 - CSME immediate focal: 15% by 3 years
 - CSME deferred focal: 30% by 3 years
 - ME, not CS, immediate focal: 8% by 3 years
 - ME, not CS, deferred focal: 14% by 3 years
- Increased chance of moderate visual acuity gain (if 20/40 or worse and fovea involved) from 5% (deferred) to 17% (immediate rx)

Laser Technique:

Part 1 (focal): Direct treatment to microaneurysms (MAs):

- 50 – 100 micron spot
- Intensity: change color of MA or retina around MA
- Duration: 0.05 – 0.10 second
- Location: areas of edema

Part 2 (Grid): Scatter (“grid”) to areas of edema not associated with MAs:

- 50 – 100 micron spot
- 1 to 2 burn widths apart
- Intensity: change color of retina or MA
- Duration: 0.07 – 0.10 second

DRCR Study: Focal Laser vs. Intravitreal Triamcinolone for DME

Multicenter, randomized clinical trial

Major Eligibility Criteria Assessed:

- ≥ 18 years old
- Type 1 or type 2 diabetes
- Center-involved DME (with OCT CSF ≥ 250 μm)
- VA letter score 73 to 24 (20/40 to 20/320)

Eligible eyes randomized
Subjects with 2 study eyes assigned alternative treatment in 2nd eye

**Focal/Grid
Laser**

**1 mg
IVT**

**4 mg
IVT**

Re-treatment (within 4 wks) unless any of the following:

- Treatment successful
- Substantial improvement in macular edema
- Adverse events or maximal treatment
- Further treatment appears futile

Efficacy Outcomes:

- Primary outcome assessment at 2 years
- Primary measure: Visual acuity (VA)
 - Scientific objective: Mean change in VA
 - Regulatory objective for FDA: Proportion with decrease in VA letter score ≥ 15
- Secondary measure: Retinal thickening on OCT

Major Eligibility Requirements:

- At least 18 years old
- Type 1 or type 2 diabetes
- Center-involved DME confirmed on OCT

- (central subfield thickness ≥ 250 microns)
- Best-corrected VA letter score 73 to 24
 - (Snellen equivalent 20/40 to 20/320)

Baseline characteristics

- Mean age: 63 years
 - Diabetes type: 5% type 1, 95% type 2
 - Visual acuity (Snellen equivalent)
 - 20/40 to 20/63: 58%
 - Worse than 20/63 to better than 20/200: 38%
 - 20/200 to 20/320: 5%
 - OCT central subfield thickness
 - Mean: 424 microns
- Range: 133 to 1164 microns

Primary Outcome: Mean Change in BCVA at 2 years

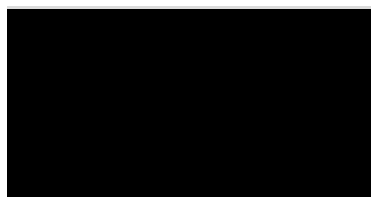
Mean Change in VA (letter score)	Laser N = 330	1 mg N = 256	4 mg N = 254
	+1	-2	-3

Pairwise Comparisons	Mean Difference*	P value*
Laser vs. 1 mg	+3.5 letters	0.02
Laser vs. 4 mg	+4.6 letters	0.002
1 mg vs. 4 mg	+1.1 letters	0.49

Change in OCT central subfield Thickness

Change in OCT CSF	Laser N=220	1 mg N=178	4 mg N=162
Mean*	-139	-86	-77
Thickening Decreased $\geq 50\%$	67%	46%	48%
Thickness <250 microns	53%	34%	38%

*Pairwise Comparisons	P value
Laser v 1 mg	<0.001
Laser v 4 mg	<0.001
1 mg v 4 mg	0.91



ADVERSE EVENTS:

IOP elevation

	Laser group	1mg IVT	4mg IVT
$\geq 10\text{mmHg}$ rise	4%	16%	33%
$>30\text{mmHg}$ rise	1%	9%	21%

Cataract Surgery

Laser group	1mg IVT	4mg IVT
13%	23%	51%

CONCLUSIONS:

- VA benefit in 4 mg IVT group at 4 months consistent with published case series
- However, no difference in VA between 4 mg IVT and laser group by 1 year
- Greater VA benefit and fewer side effects (IOP and cataract) in laser group at 2 years, and sustained effect thru 3 years
- OCT results mirrored VA results
- Results re-affirm importance of laser in management of DME
- Focal/grid should be used for DME regardless of:
 - Baseline visual acuity
 - Baseline CSF thickness
 - Prior macular photocoagulation for DME
 - Phakic or pseudophakic
- Focal/grid currently benchmark for clinical trials for DME
-

Diagnosis of Diabetic Macular Edema

Sophie J. Bakri, MD
Associate Professor of Ophthalmology
Vitreoretinal Diseases and Surgery
Mayo Clinic
Rochester, MN

Diabetic macular edema (DME) is the commonest cause of visual loss in diabetic retinopathy. It is important to accurately diagnose it, quantify its extent and differentiate it from other entities.

The gold standard for diagnosing DME has been to perform slit lamp biomicroscopy of the posterior pole using a contact lens. It is important to characterize:

- presence of cystoid macular edema
- location of retinal thickening relative to the fovea
- presence and location of lipid exudates.

A combination of these 3 criteria make up the definition of **Clinically Significant Macular Edema**, defined by the ETDRS study. The ETDRS used CSME as the criterion for treatment with focal laser photocoagulation.

Definition of Clinically Significant Macular Edema

1. Retinal edema located at or within 500 microns of the fovea
2. Hard exudates at or within 500 microns of the fovea, if associated with thickening of adjacent retina
3. An area of retinal thickening greater than 1 disc area, if located within 1 disc area of the center of the macula.

Use of fluorescein angiography in Diabetic Macular Edema

Fluorescein angiography is used as an adjunct to clinical examination in the diagnosis of macular edema. It identifies the source and severity of DME. It aids in classifying DME into focal and diffuse types. Depending on the type of DME, the response to laser and pharmacologic treatments can be different; therefore classification is important to ensure optimal treatment. Microaneurysms can be more accurately targeted with laser treatment. FA also identifies capillary nonperfusion and the extent of the foveal avascular zone, thereby describing the extent of retinal ischemia.

Use of OCT in Diabetic Macular Edema

OCT is used to classify DME into various subtypes, including:

- cystoid macular edema
- diffuse macular edema
- macular edema with subretinal fluid
- macular edema with epiretinal membrane
- macular edema with posterior hyaloidal traction

In addition, SD-OCT can show underlying RPE atrophy which may limit the prognosis for treatment.

It is important to look at the vitreoretinal interface in DME, as this may alter treatment strategies. With the different treatment strategies available including focal/grid laser, intravitreal anti-VEGF agents, intravitreal and periocular steroids, pars plana vitrectomy, and combination treatment, it is important to correctly classify DME in order to decide on the optimal treatment algorithm for the patient.

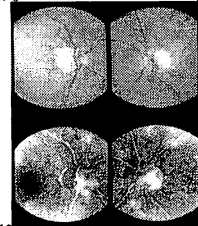
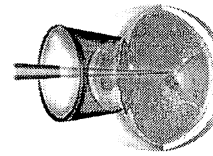
Application of Recent Clinical Trials Results to Management of Proliferative Diabetic Retinopathy

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Director of the Retina Service
AAO Annual Meeting 2009

Proliferative Diabetic Retinopathy

- Laser photocoagulation highly effective in causing regression of PDR
- Cuts risk of severe visual loss 50 %



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DRS Study. Ophthalmology 1978;85:82-106.

Proliferative Diabetic Retinopathy

PRP side effects

- 5-10 % chance of decreased reading vision
- Decreased visual field
- Decreased night vision
- ? Increase in DME

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DRS Study. Ophthalmology 1978;85:82-106.

Proliferative Diabetic Retinopathy

New information in management of PDR:

- Single versus multiple session PRP
- Adjunctive use of anti-VEGF, steroids
- Concurrent DME and PDR management

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The Diabetic Retinopathy Clinical Research Network

An Observational Study of the Development of Diabetic Macular Edema Following Panretinal (Scatter) Photocoagulation (PRP) Given in 1 or 4 Sitzings

Sponsored by the National Eye Institute,
National Institutes of Health, U.S. Department of Health and Human Services.



Background:

Panretinal Photocoagulation (PRP) for PDR

- PRP is the standard treatment of PDR
- Usually performed over 1 or more sittings (ETDRS 2 or more sittings)
- 2004 survey of DRCR.net investigators: one-quarter routinely use one sitting for PRP

PRP and Macular Edema

- PRP associated complications include macular edema
 - ETDRS - 18% developed macular edema 4 months after full PRP (1200 – 1600 spots)
- Theories:
 - Oncotic fluid accumulation related to tissue destruction
 - PRP induced inflammation leading to cytokine release and increased permeability of the retinal capillaries

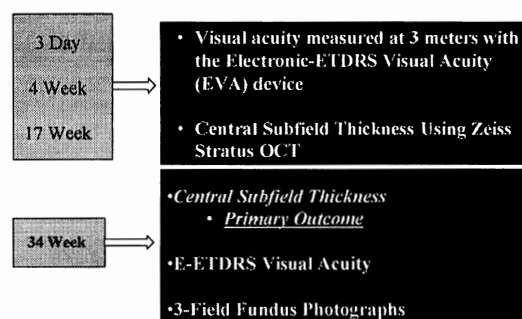
What are Some Pros and Cons of Delivering PRP in 1 Sitting?

- Pros
 - Convenience
 - Completion before complications occur (VH)
- Cons (theoretical):
 - May cause macular edema with VA loss
 - Greater patient discomfort
 - Need for retrobulbar or peribulbar anesthetic
 - Higher risk of acute pressure rise, angle closure, or choroidal effusion

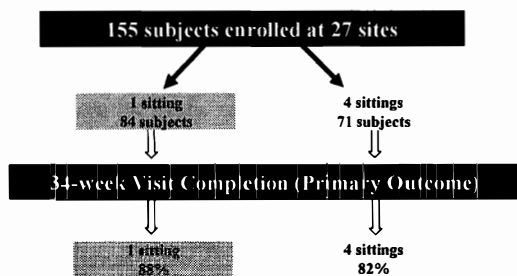
Primary Study Objective

- Determine the incidence of new macular edema on OCT, following PRP in diabetic eyes without center edema at 34 weeks
- To compare the incidence of macular edema with a 1-sitting versus 4-sitting regimen

Outcome Assessment



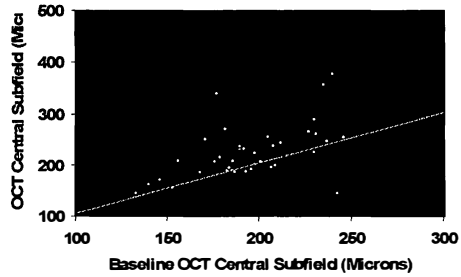
Study Enrollment



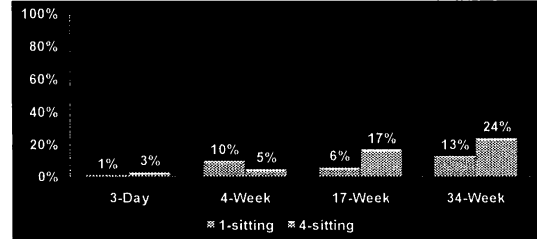
Central Subfield Thickness

	1-sitting	4-sitting	P value
<i>Baseline</i>	207 μ	198 μ	
<i>Change from baseline - median microns</i>			
3d	+9	+5	0.01
4wks	+13	+5	0.003
17wks	+14	+15	0.08
34wks	+14	+22	0.06

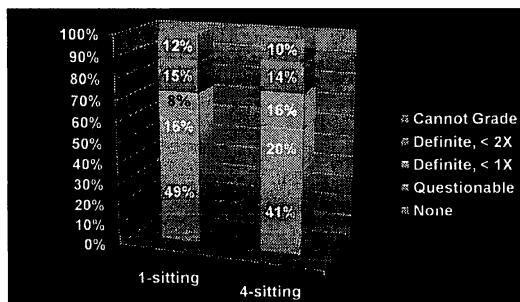
Central Subfield Retinal Thickness: 34 Weeks vs. Baseline



CSF ≥ 250 Microns and Change from Baseline ≥ 25 Microns



Macular Edema on Fundus Photos at 34 weeks



Treatment of DME

- One eye in each group was treated for DME prior to 34 weeks
- No difference in final outcome

Laser-Ranibizumab-Triamcinolone for DME Plus PRP Study DRCR.net Protocol J

Sponsored by the National Eye Institute, National Institutes of Health, U.S. Department of Health and Human Services

Study Objective

- To determine whether intravitreal anti-VEGF drug or intravitreal corticosteroid can reduce the risk of VA loss following PRP in eyes with DME.

Major Eligibility Criteria

- Age ≥ 18 years.
- Type 1 or type 2 diabetes
- Study eye with
 - Severe NPDR or PDR for which the investigator intends to perform full PRP
 - OCT central subfield thickness $\geq 250\mu$
- Subjects may have only one study eye.

Treatment Groups

- 381 eyes randomized to either:
 - 0.5 mg intravitreal ranibizumab (Lucentis™) at baseline and 4 weeks
 - 4 mg intravitreal triamcinolone acetonide at baseline and sham injection at 4 weeks
 - Sham injection at baseline and 4 weeks
- All groups receive focal laser and PRP (1200-1600 burns).

Treatment Regimen

- 1st injection at randomization
- Focal laser at 3-10 day visit
- 1st PRP sitting on day of focal or within 14 days of injection
- 2nd injection at 4 weeks
- Completion of PRP by 49 days (1 – 3 sittings)

Follow-up Schedule

- Phase 1
 - 1, 4, and 14-week visits
- Phase 2
 - 34 and 56-week visits
 - Treatment for DME at investigator discretion
 - Additional PRP not given unless DR worsens

Main Efficacy Outcomes

- Primary Outcome:
 - VA at 14 weeks.
- Secondary Outcomes at 14 Weeks:
 - Change in OCT central subfield and retinal volume
 - Presence and extent of new vessels on fundus photographs
 - Vitreous hemorrhage
 - Additional sessions of scatter photocoagulation due to worsening DR

Main Safety Outcomes

- Injected-related:
 - Endophthalmitis, retinal detachment
- Ocular drug-related:
 - Inflammation, cataract, cataract surgery, increased IOP, glaucoma medications, glaucoma surgery
- Systemic drug-related:
 - Cardiovascular events

Macugen for PDR

- Sham injection or intravitreal pegaptanib (0.3 mg, 1 mg, 3 mg) at study entry, week 6, and week 12
- Additional injections and/or focal laser as needed during the ensuing 18 weeks, up to a maximum of 6 pegaptanib/sham therapies
- 172 eyes: 19 with PDR

Adams AP et al. Diabetic Retinopathy Study Group. Changes in retinal neovascularization after pegaptanib therapy in diabetic individuals. *Ophthalmology*. 2006 Jan;113(1):23-8.

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Macugen for PDR

- 16 of 19 had follow-up photos and no recent PRP
- Regression of PDR on fundus photos or regression/ absence FA leakage at 36 weeks:
 - 8 of 13 (62%) pegaptanib treated eyes
 - 0 of 3 in the sham group
 - 0 of 4 fellow (nonstudy)

Adams AP et al. Diabetic Retinopathy Study Group. Changes in retinal neovascularization after pegaptanib therapy in diabetic individuals. *Ophthalmology*. 2006 Jan;113(1):23-8.

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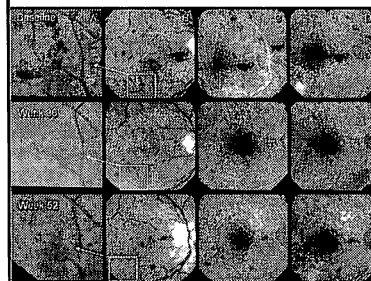
Macugen for PDR

- In 3 of 8 with regression, PDR progressed at week 52 after cessation of pegaptanib at week 30.

Adams AP et al. Diabetic Retinopathy Study Group. Changes in retinal neovascularization after pegaptanib therapy in diabetic individuals. *Ophthalmology*. 2006 Jan;113(1):23-8.

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Macugen for PDR



Second row: At week 36, after 6 periodic pegaptanib injections and 6 weeks since last injection, there is regression of NVE and less apparent MAs (C), and regression of leakage from NVE in the late phase (D). Third row, Fifty-two weeks after study entry and 22 weeks since the last pegaptanib injection, there is seen reappearance of NVE and reappearance of leakage

Adams AP et al. Diabetic Retinopathy Study Group. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology*. 2006 Jan;113(1):23-8.

Avastin for PDR

- PACORES Collaborative Group
- 1,173 patients with 12 month follow-up: 159 with PDR
- 7 eyes with progressive PDR despite laser:
 - Regressed within days
 - 6 developed TRD or progression of TRD due to fibrosis
- Repeat injections were safe and tolerated

Wu et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). *Graciles Arch Clin Exp Ophthalmol*. 2008 Jan;246(1):81-7.

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When to Refer for Surgery ?

- NVI without prior laser PRP - urgent
- Unresponsive to PRP
- Persistent vitreous hemorrhage
- Traction retinal detachment
 - Macula off
 - Macula threatened

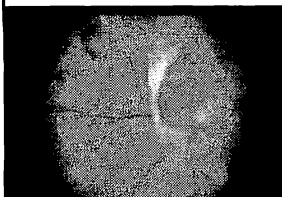


DVRS Ophthalmology 1988;95:1307. DVRS Ophthalmology 1988;95:1321. DVRS. Early PPV's. *Arch Ophthalmol* 1990;108:958.

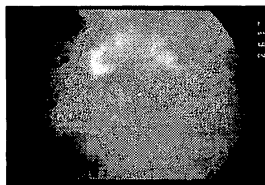
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Traction Retinal Detachment

- Retinal elevation
- Fibrovascular tissue



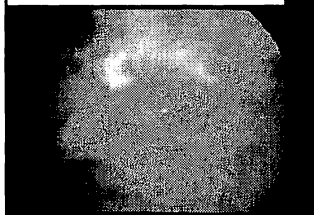
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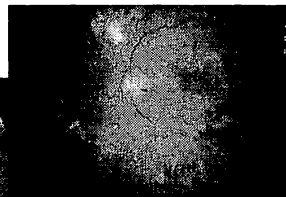
- Requires Surgery

Traction Retinal Detachment

- Pars Plana Vitrectomy



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Thank You!

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