

Front Line Diabetic Retinopathy

What Not to Miss and Why

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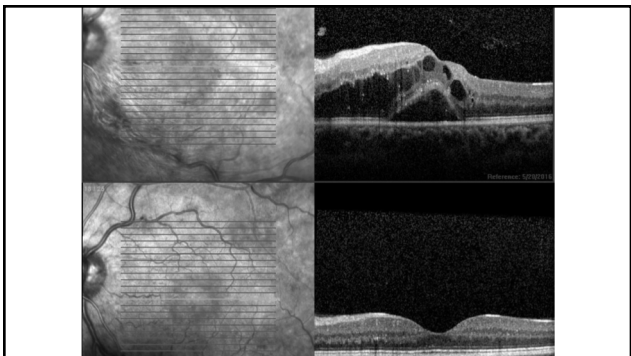
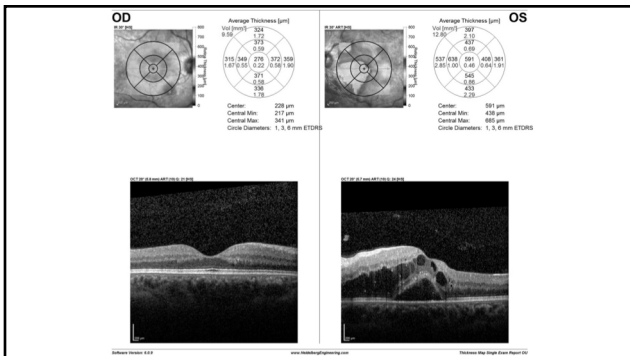
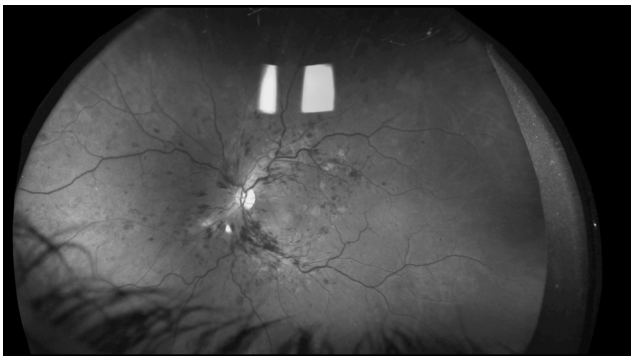
Relevant Disclosures

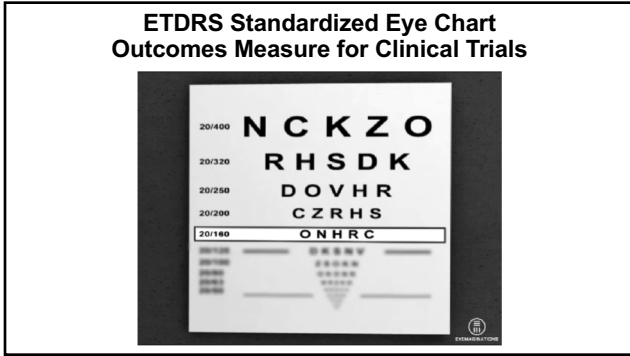
- Consultant / Grant Support: Allergan, Apellis, Genentech / Roche, Novartis, Regeneron, REGENXBIO, Adverum, Clearside Biomedical, Opthea, Samsung, Santen, Bayer, Senju, Zeiss, Heidelberg, OHR, BioTime, Gemini, Chengdu Kanghong Biotechnology, Optos, Kodiak Sciences, Johnson & Johnson
- Co-patent holder on OPTOS de-warping algorithms

DMB had full control of the presentation

Case Study 1

- 57 Year Old Female "Blurry Vision OS"
- Diabetic for 15 years- Hemoglobin A1c = 9.2
- Refraction- Plano OD-20/25 +1.50 OS- 20/60





Early Treatment Diabetic Retinopathy Study

Photocoagulation for Diabetic Macular Edema
Early Treatment Diabetic Retinopathy Study Report Number 1
Early Treatment Diabetic Retinopathy Study Research Group

Abstract

Background: The purpose of this study was to determine whether photocoagulation of the macula in eyes with macular edema and mild to moderate diabetic retinopathy improved visual acuity compared with observation.

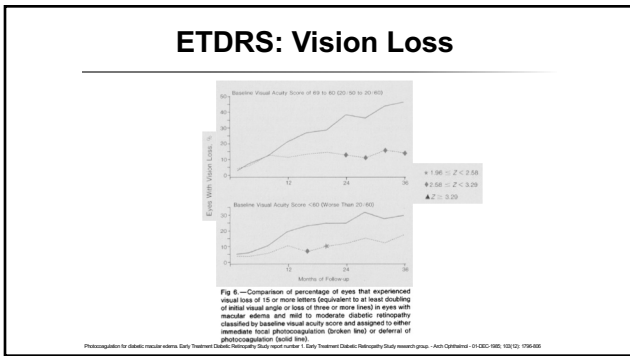
Methods: The study was a randomized, controlled trial. The study population consisted of 105 eyes with macular edema and mild to moderate diabetic retinopathy. The study was conducted in two phases. In the first phase, 53 eyes were randomized to receive photocoagulation and 52 eyes were randomized to receive observation. In the second phase, 52 eyes were randomized to receive photocoagulation and 53 eyes were randomized to receive observation.

Results: The mean duration of follow-up was 3.6 years. The mean visual acuity at baseline was 20/400 in the photocoagulation group and 20/400 in the observation group. At the end of follow-up, the mean visual acuity was 20/200 in the photocoagulation group and 20/400 in the observation group. The difference in visual acuity between the two groups was statistically significant (P < 0.001).

Conclusions: Photocoagulation of the macula in eyes with macular edema and mild to moderate diabetic retinopathy improved visual acuity compared with observation.

Vision Gain

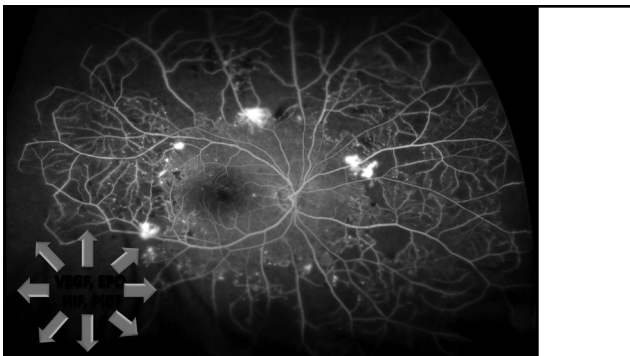
Fig 7—Comparison of percentage of eyes that experienced visual gain of one or more letters (equivalent to three lines) in eyes with macular edema and mild to moderate diabetic retinopathy assigned to either immediate focal photocoagulation (broken line) or deferral of photocoagulation (solid line).



Macular Laser for DME

- Standard of care 1985-2012
- No impact on underlying disease progression
- Reduces risk of vision loss, but few patients experience visual improvement

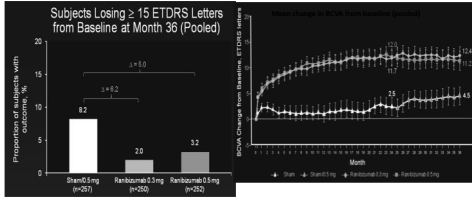
Focal Laser Grid Laser Courtesy of Dr Donald D'Amico



Anti-VEGF Key Studies: Ranibizumab

- RISE/RIDE: 2 parallel phase III, multicenter, double-masked, sham-injection controlled, randomized studies
- Assessed safety and efficacy of intravitreal ranibizumab for the treatment of DME
- In the third year, patients who had received sham therapy were eligible to switch to treatment with ranibizumab

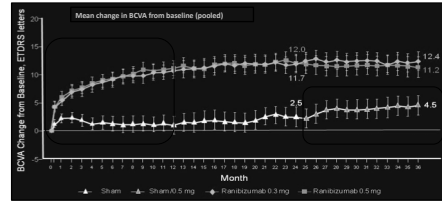
Sustained Improvement With Ongoing Anti-VEGF Therapy



- Severe VA loss (15 letters) significantly reduced
- Rapid improvements in vision & anatomy maintained for 3 years

Brown D et al. RISE and RIDE Research Group. Ophthalmology. 2013;120:2013-2022.

Effects of Treatment Delay



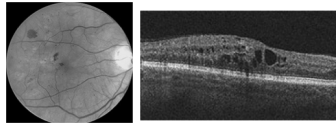
- With crossover to 1 year of 0.5 mg ranibizumab therapy at third year, original sham treatment group's visual gains were lower than those seen in first year of ranibizumab-treated groups (2.8 vs 10.6 and 11.1 letters)

- Delayed treatment reduced magnitude of VA benefits of anti-VEGF therapy

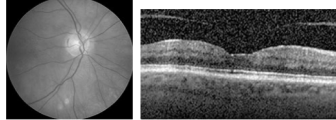
Brown D et al. RISE and RIDE Research Group. Ophthalmology. 2013;120:3013-3022.

56-year-old Male With DME Treated With Monthly Ranibizumab

Baseline
Snellen = 20/100



Month 36
Snellen = 20/50



First FDA Approved Medication for DME

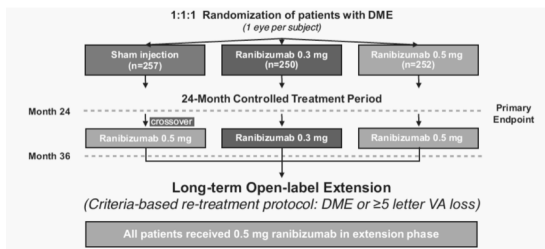


August 10, 2012

- First & only FDA approved medication for DME
- Changed the standard of care for the first time in > 25 years

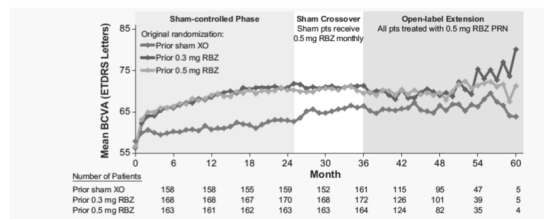


Open Label Extension RISE/RIDE



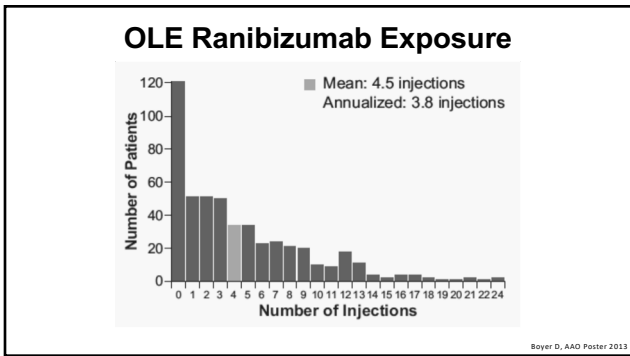
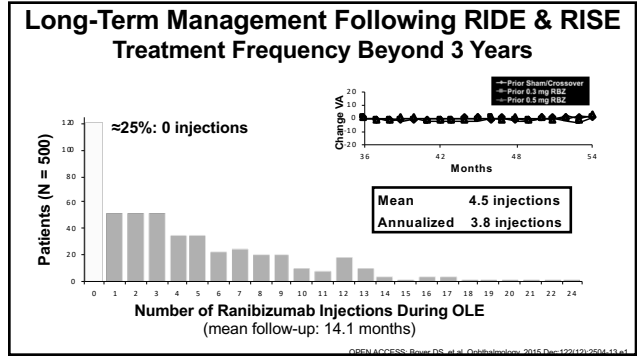
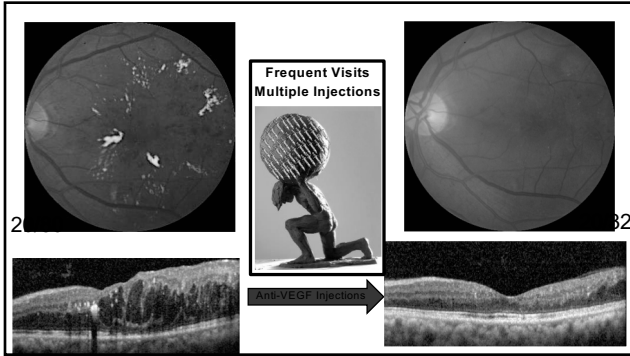
Boyer D, AAO Poster 2013

OLE Maintenance of Vision



* Data became unavailable after Month 54 due to the low number of patients at that point. BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = as-needed; pts = patients; RBZ = ranibizumab; XO = treatment crossover.

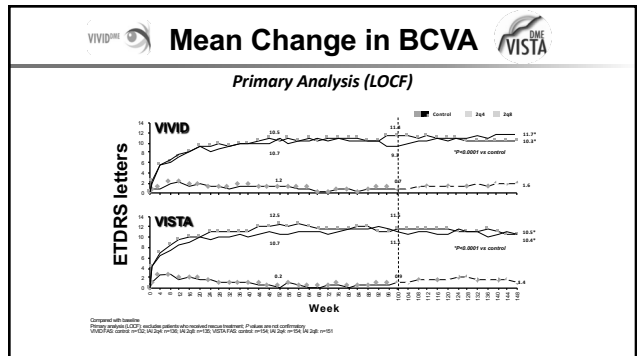
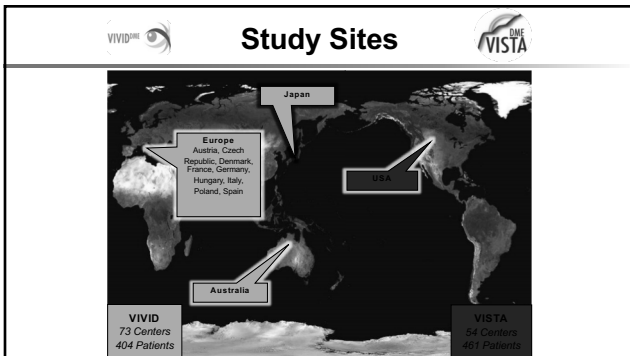
Boyer D, AAO Poster 2013

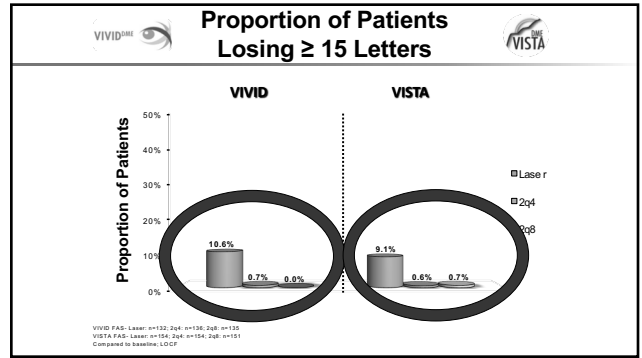
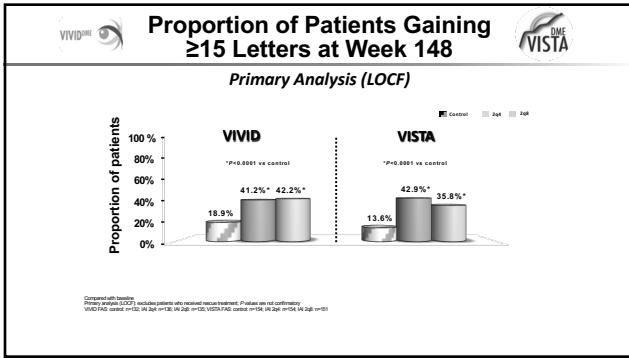


Anti-VEGF Key Studies: Aflibercept

- VIVID-DME and VISTA-DME: assessed safety and efficacy of aflibercept vs laser alone in the treatment of DME
- Treatment groups: intravitreal aflibercept monthly, every 2 months (after 5 initial monthly injections), or laser photocoagulation

Korabelnik JF, Brown DM, et al. Ophthalmology. 2014 Jul 8.





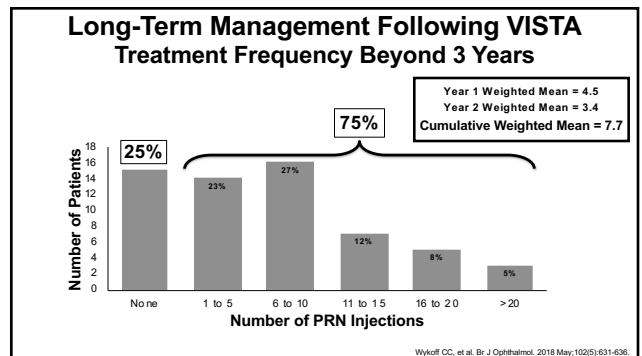
U.S. Food & Drug Administration
FDA Approved

July 29, 2014
Diabetic Macula Edema

EYLEA® (aflibercept) Injection
For Intravitreal Injection

2 mg/0.05 mL (40 µg/0.05 mL)

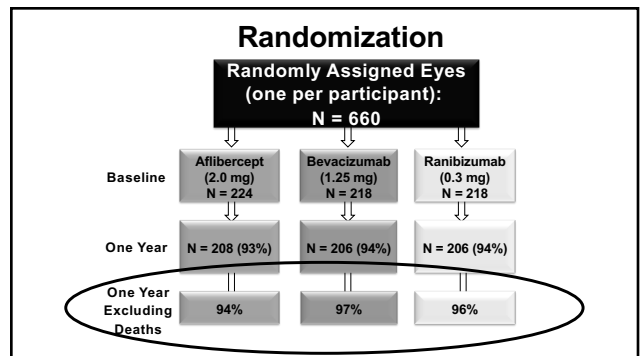
- Each carton contains 2 mL glass vial of EYLEA.
- Each vial contains 20 mg aflibercept. Other needles to be used for intravitreal injection.
- Each 2 mL glass vial is to be used for intravitreal injection.
- Each 2 mL plastic syringe for intravitreal injection.
- Each syringe is to be used for intravitreal injection.



Diabetic Retinopathy Clinical Research Network

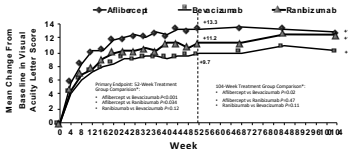
Comparative Effectiveness Study of Aflibercept, Bevacizumab, or Ranibizumab for DME

Supported through a cooperative agreement from the
National Eye Institute; National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health, Department of Health and Human Services EY142231, EY142229, EY018817



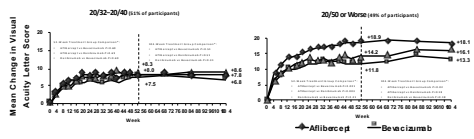
Visual acuity gains varied based on anti-VEGF at the primary endpoint of 1 year and were maintained through 2 years^{1,2}

Overall Mean Change in Visual Acuity Letter Score from Baseline to 2 Years



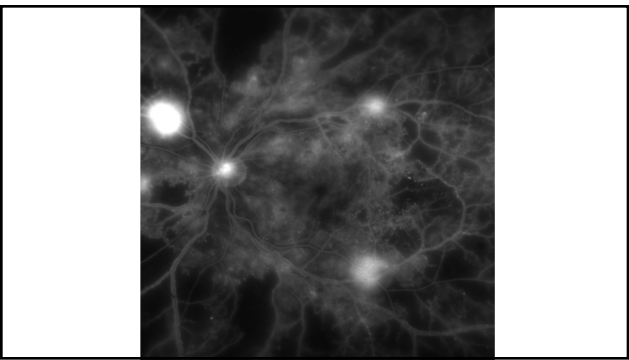
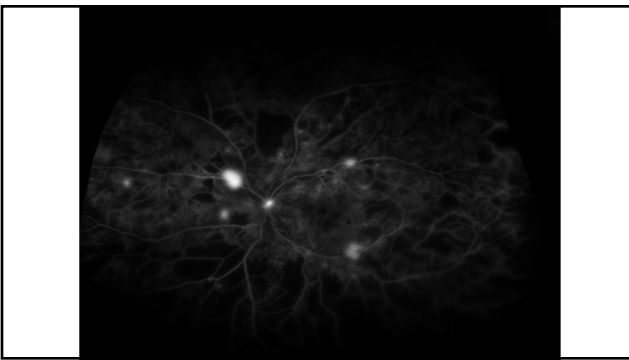
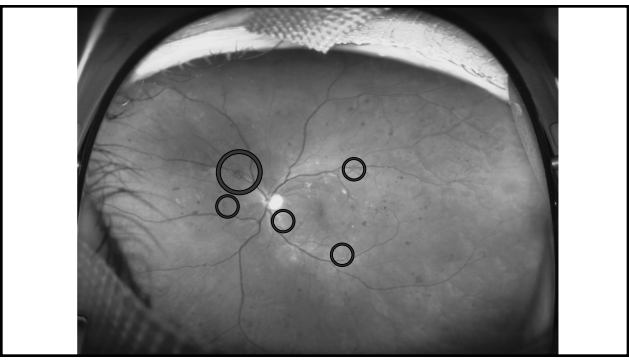
Visual acuity gains varied by baseline visual acuity

Mean Change in Visual Acuity Letter Score from Baseline to 2 Years by Baseline Visual Acuity




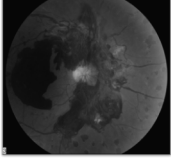
Case Study 2

- 35 Year Old Male- Failed DPS test- "Just need glasses"
- Diabetic for 5 years- Hemoglobin A1c = Unknown
- Doesn't want dilation- "Need to work tonight"
- Refraction- -1.25 ish 20/25 OU



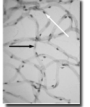
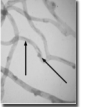
Diabetic Retinopathy

- 25% of patients with diabetes have some retinopathy
 - 5,000,000 in US
- Leading cause of visual loss & new-onset blindness 20 – 64

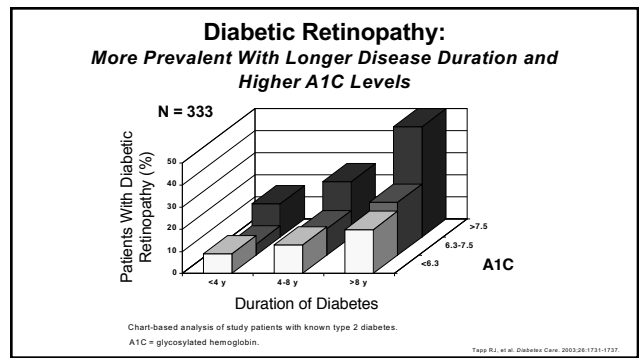
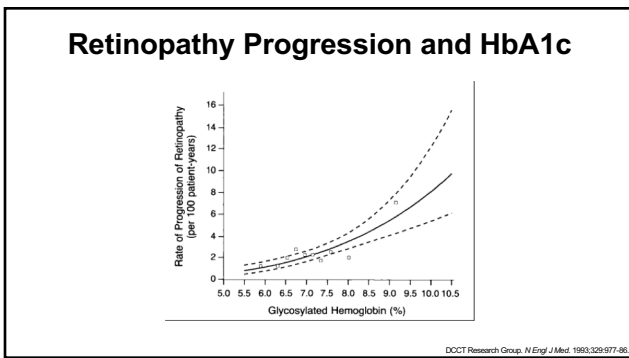



Pathophysiology of Diabetic Retinopathy

- Capillary pericyte loss
- Endothelial cell loss
- Nonfunctional acellular capillaries
- Capillary basement membrane thickening
- Microaneurysm formation
- Neovascularization

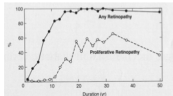
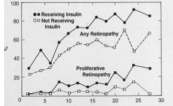



Frank RN. Etiologic mechanisms in diabetic retinopathy. In: Ryan SJ, ed. *Retina*. Schachar AP and Murphy RP, eds. vol. 2. Medical Retina, St. Louis, 1994. Mosby. 1253-1265. Photos copyright acknowledgement to publication.



Prevalence of Proliferative Retinopathy

- Type I DM
 - 15 years' duration: 30%
- Type II DM
 - Receiving insulin:
 - 15 years' duration: 15%-20%
 - Not receiving insulin:
 - 15 years' duration: 5%-10%

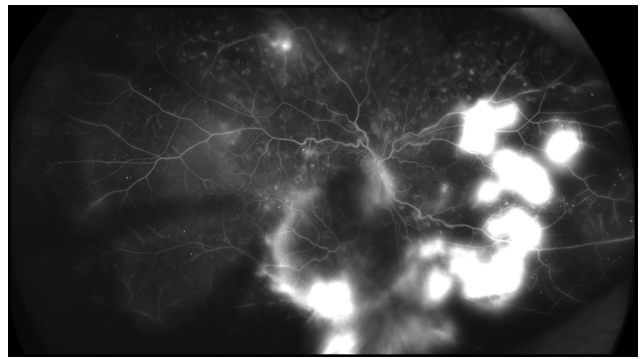
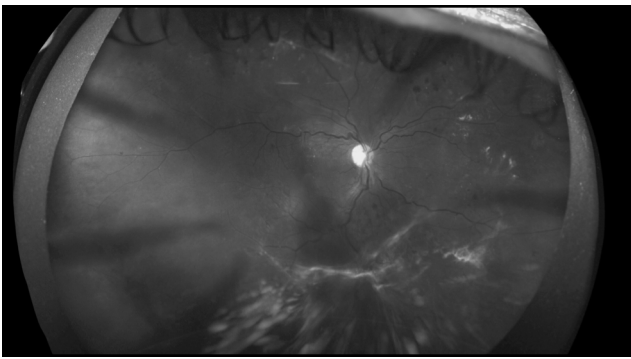
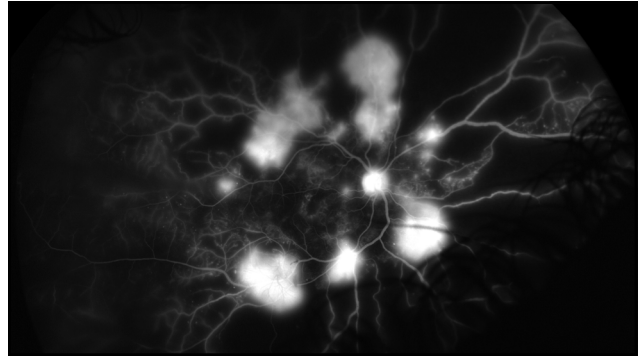
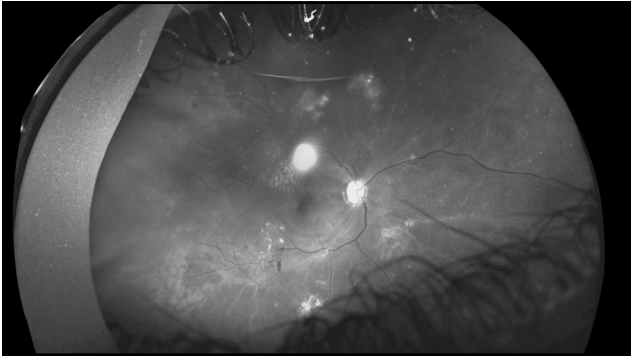




Redrawn from Klein R, Klein BEK, et al. *Arch Ophthalmol* 102:520-526, 1984. In Frank RN. Etiologic mechanisms in diabetic retinopathy. In: Ryan SJ, ed. *Retina*. Schachar AP and Murphy RP, eds. vol. 2. Medical Retina, St. Louis, 1994. Mosby, p. 1253-1265.

Treatments > 90% Effective at Preventing Blindness




Earlier Tx = Better Outcomes



 **Protocol S**

Five-Year Outcomes of Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy:
Randomized Clinical Trial

   **DRCR.net**

Study Design

Randomized, multi-center clinical trial (55 Sites)

Study eye(s) meeting all of the following criteria (*a participant can have 2 study eyes*):

- PDR
- No history of PRP
- Best corrected visual acuity letter score ≥ 24 (~Snellen equivalent 20/320 or better)
- Eyes with or without central-involved DME were eligible

Primary Objective: Compare the efficacy and safety of PRP with that of intravitreal ranibizumab (0.5-mg in 0.05 mL) for proliferative diabetic retinopathy (PDR)

Diabetic Retinopathy Clinical Research Network (DRCR.net): http://publicfiles.jaeb.org/drcrnet/presentations/DRCRS11ASRS7_18_18.pptx

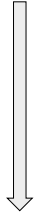
Five-Year Outcomes of Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy

- **PRP**
 - Baseline then additional PRP if “size or amount of NV increased”
- **Ranibizumab**
 - Q4 through W24 with deferral option at W16 & W20 if “NV resolved”
 - After W24 = Q4 if NV “improved or worsened,” deferral if NV “resolved or stable after 2 consecutive injections”

Gross JG, et al. JAMA Ophthalmol. 2018;136(10):1138-1148

**Mean Number of Injections
5-Year Completers Only**

	Ranibizumab Group (N = 117)	PRP Group (N = 123)
Year 1	7.1	2.3
Year 2	3.3	1.1
Year 3	3.0	0.9
Year 4	2.9	0.6
Year 5	2.9	0.4
Cumulative Through 5 Years	19.2	5.4



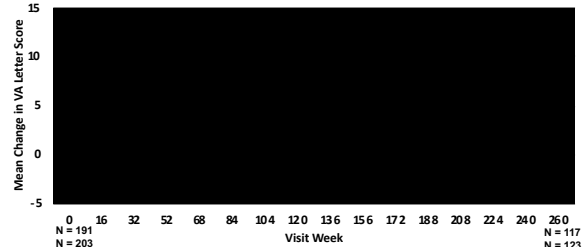
Diabetic Retinopathy Clinical Research Network (DRCR.net). http://publicfiles.jeeb.org/drcrnet/presentations/DRCS11ASRS7_18_18.pptx

Visual Acuity at 5-Years

	Ranibizumab (N = 117)	PRP (N = 123)
Visual Acuity		
Mean letter score	80	81
~Snellen Equivalent, Mean	20/25	20/25
Median letter score (25 th , 75 th percentile)	84 (89, 78)	84 (89, 77)
~Snellen Equivalent, Median	20/20 (20/16, 20/32)	20/20 (20/16, 20/32)

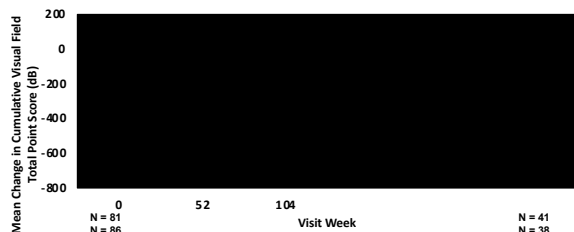
Diabetic Retinopathy Clinical Research Network (DRCR.net). http://publicfiles.jeeb.org/drcrnet/presentations/DRCS11ASRS7_18_18.pptx

Mean Changes in VA From Baseline Over Time - Overall Cohort



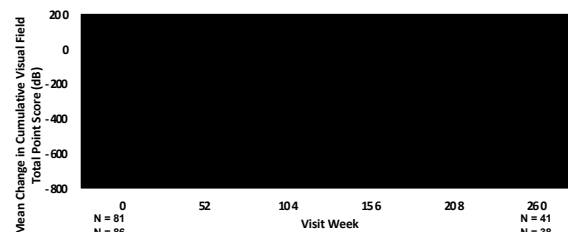
Outlying values were truncated to 3 SD from the mean. Diabetic Retinopathy Clinical Research Network (DRCR.net). http://publicfiles.jeeb.org/drcrnet/presentations/DRCS11ASRS7_18_18.pptx

Mean Change in Cumulative Visual Field Total Point Score (30-2 + 60-4) - Overall Cohort



Outlying values were truncated to 3 SD from the mean. Diabetic Retinopathy Clinical Research Network (DRCR.net). http://publicfiles.jeeb.org/drcrnet/presentations/DRCS11ASRS7_18_18.pptx

Mean Change in Cumulative Visual Field Total Point Score (30-2 + 60-4) - Overall Cohort



Outlying values were truncated to 3 SD from the mean. Diabetic Retinopathy Clinical Research Network (DRCR.net). http://publicfiles.jeeb.org/drcrnet/presentations/DRCS11ASRS7_18_18.pptx

DR Adverse Events: Over 5 Years

	Ranibizumab (N = 117)	PRP (N = 123)	Adjusted Difference (95% CI)
Any Retinal detachment, %	6%	15%	-9% (-14%, -4%)
Retinal Detachment involving Center of the Macula, %	1%	4%	-3% (-7%, 0%)
Neovascular Glaucoma, %	3%	4%	-2% (-6%, 2%)
Neovascularization of the Iris, %	3%	1%	1% (-1%, 3%)
Vitreous Hemorrhage, %	48%	46%	2% (-6%, 11%)
Vitrectomy, %	11%	19%	-7% (-14%, -1%)

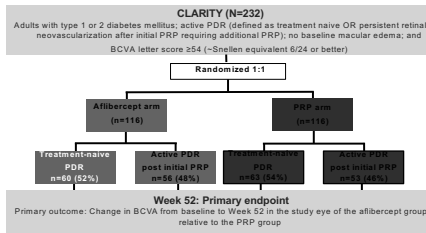
Diabetic Retinopathy Clinical Research Network (DRCR-net). http://publibfiles.jeb.org/drcrnetpresentations/DRCRS11ASRS7_18_18.pptx

CLARITY: 22 UK Centers Phase 2b Trial

- PRP versus aflibercept for PDR
 - Included treatment naïve PDR (53%) and patients with PDR previously treated with PRP (47%)
 - Different from Protocol S which only included treatment naïve
 - Excluded patients with DME
 - Different from Protocol S which included both PDR with and without DME

Sivaprasad S, et al. *BMJ Open*. 2015;5(9):e008405.

CLARITY: Study Population



BCVA, best corrected visual acuity; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation. Sivaprasad S, et al. *BMJ Open*. 2015;5(9):e008405.

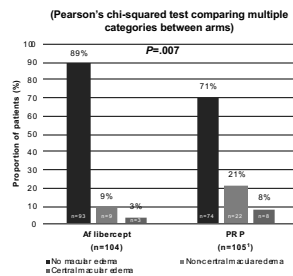
CLARITY VA Results

- At 52-weeks (primary outcome):
 - BCVA difference between groups = 4 letters ($P < .001$)
 - Laser group lost 2.9 letters
 - Aflibercept group gained 1.3 letters
- At 12-weeks (secondary outcome):
 - BCVA difference between groups = 2.3 letters
 - Laser group lost 0.9 letters
 - Aflibercept group gained 1.5 letters

Sivaprasad S, et al. *Lancet*. 2017;389(10085):2193-2203.

Other Findings in CLARITY: Presence of Macular Edema at Week 52

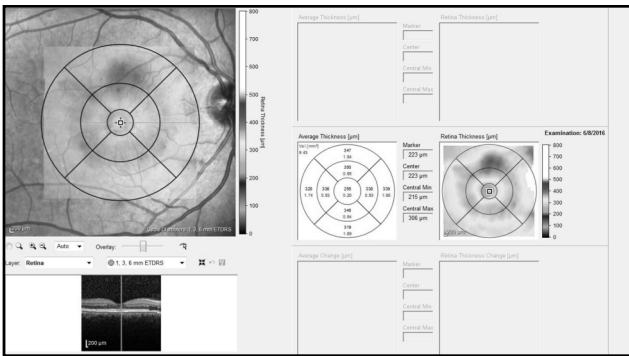
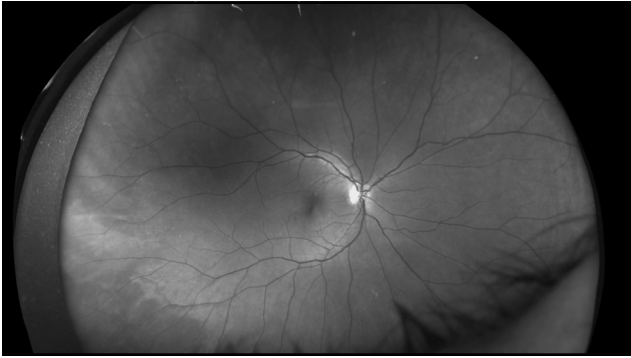
- CST and cube volume increased significantly in the PRP group compared to aflibercept
- At 52-weeks:
 - 89% of patients in the aflibercept group did not have CME
 - 71% of patients in the PRP group did not have CME



1. Two participants with missing data. Sivaprasad S, et al. *Lancet*. 2017;389(10085):2193-2203.

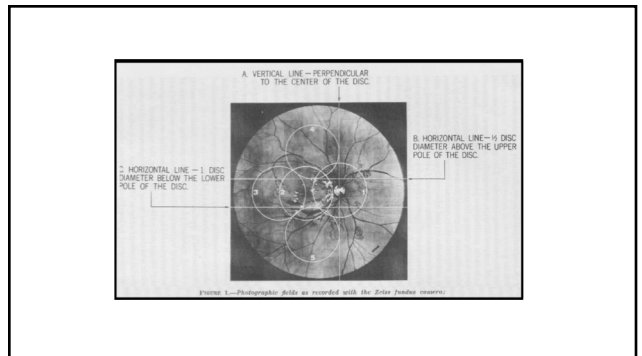
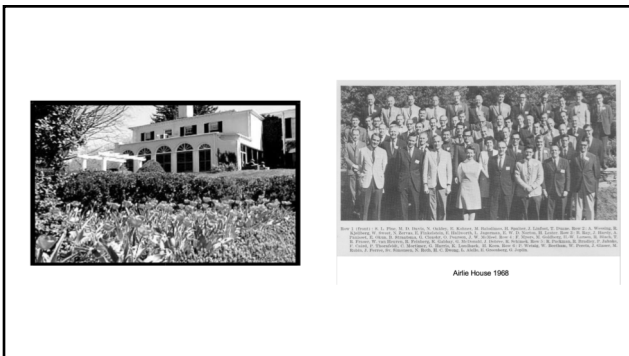
Case Study 3

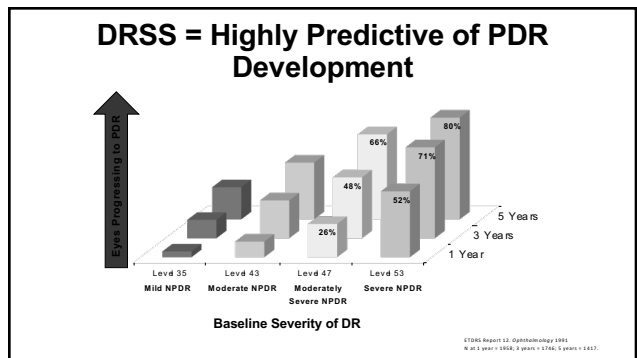
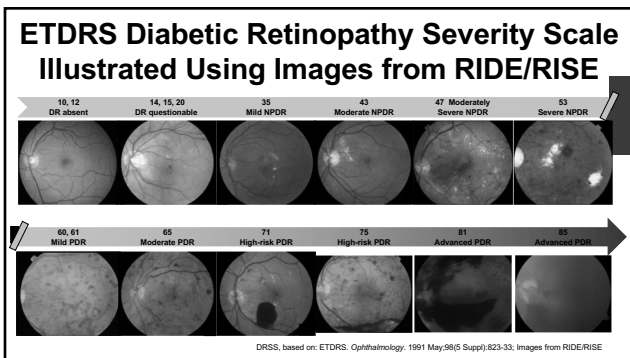
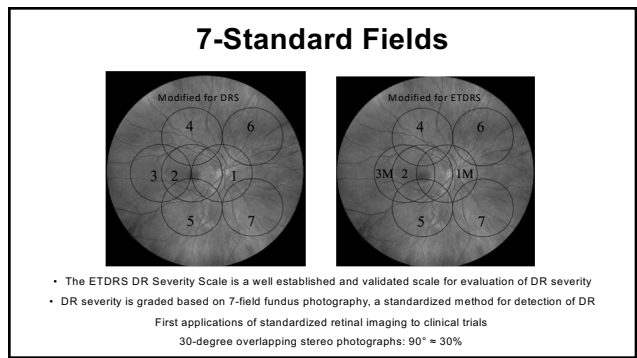
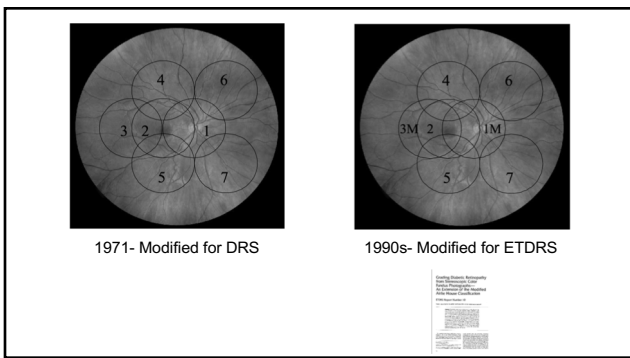
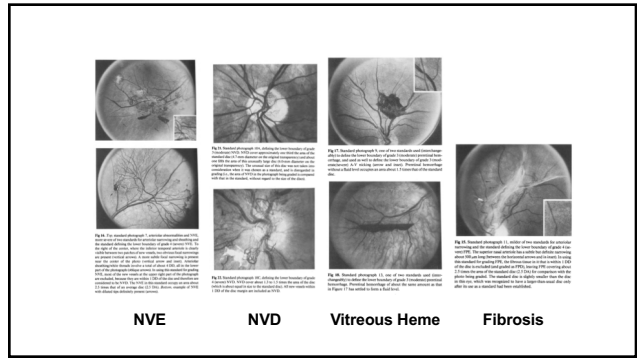
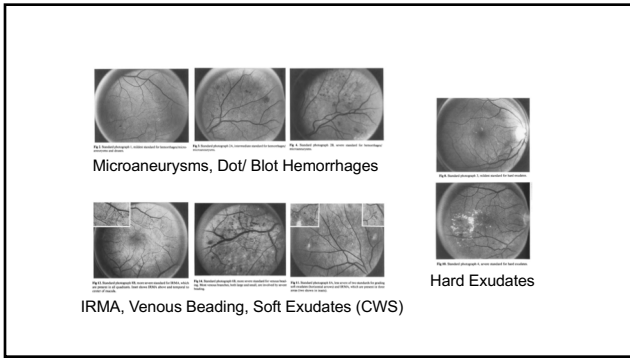
- 42 Year Old School Teacher- "Annual Exam"
- Diabetic for 12 years- Hemoglobin A1c = 8.1
- Refraction- --2.50- 20/20 OU

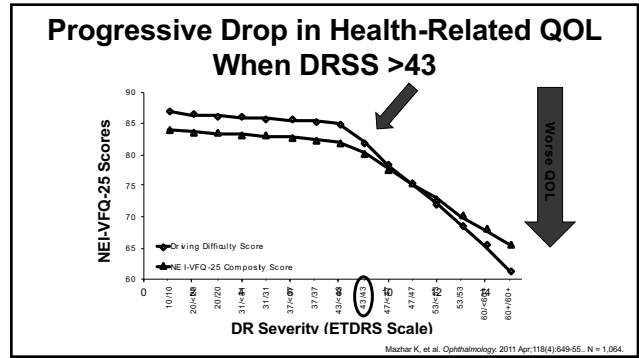
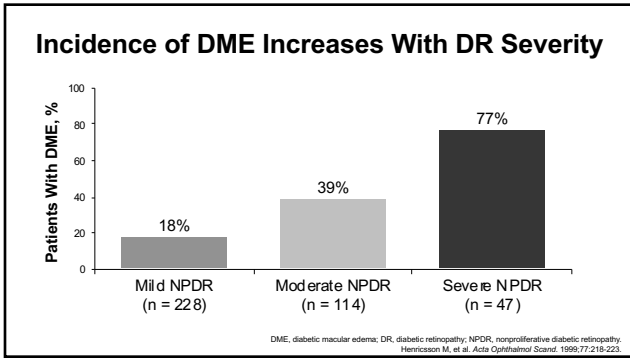


Classification of Diabetic Retinopathy

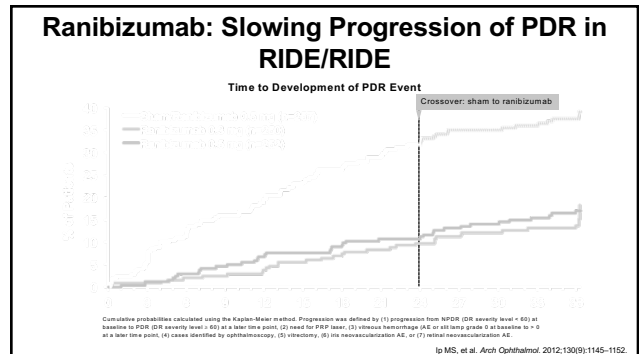
Non-Proliferative DR	Diabetic Macular Edema	Proliferative DR
 Microvascular damage <ul style="list-style-type: none"> Chronic, occurring over years Typically no significant vision loss, but progresses to DME and/or PDR Similar damage occurs in other end-organ vascular beds 	 Swelling in central retina <ul style="list-style-type: none"> Accounts for most vision loss Co-exists with NPDR and PDR 	 End stage <ul style="list-style-type: none"> Neovascularization of retina High risk of severe visual loss
More common Less severe		Less common More severe



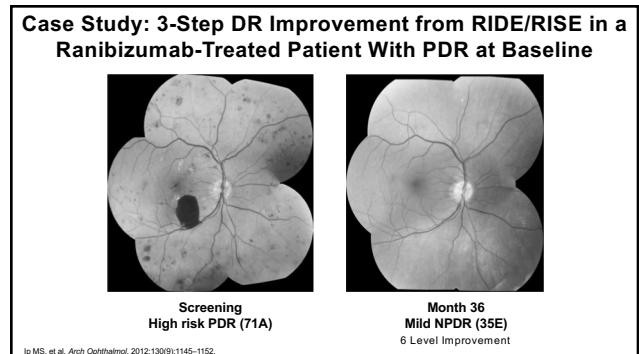


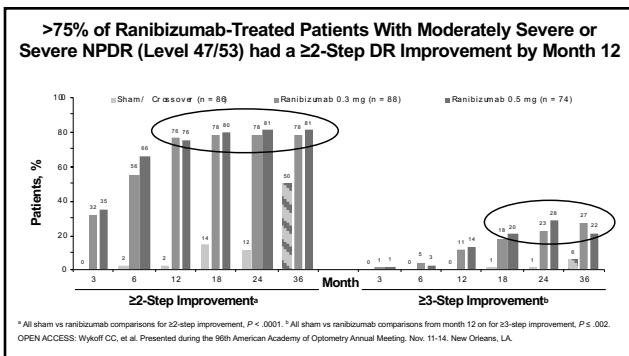
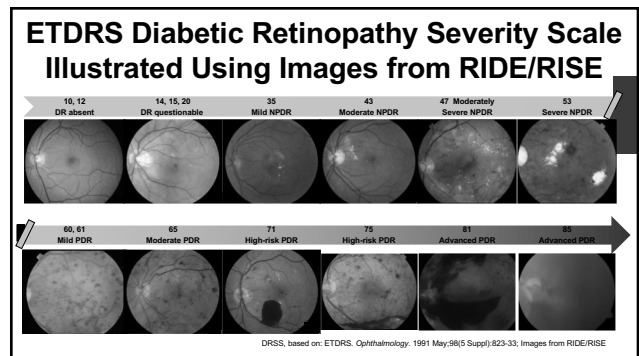
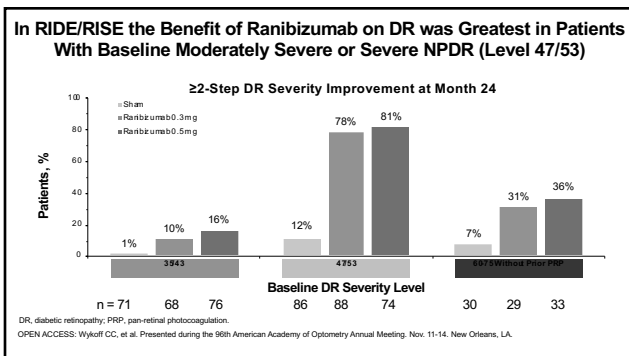
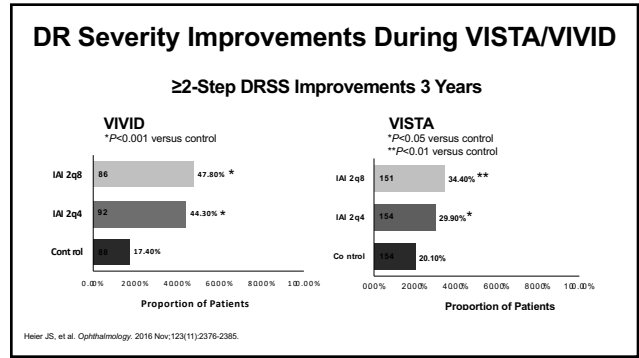
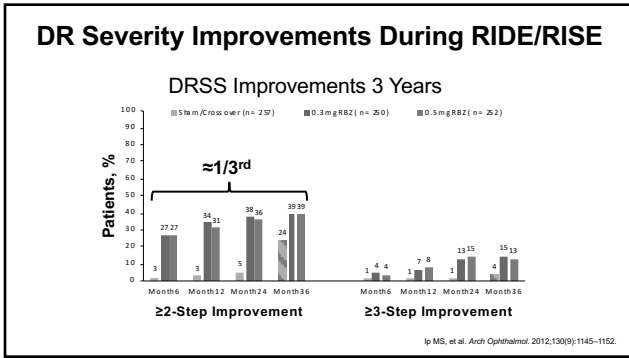


Pharmaceutical Dosing Can Slow Progression to PDR



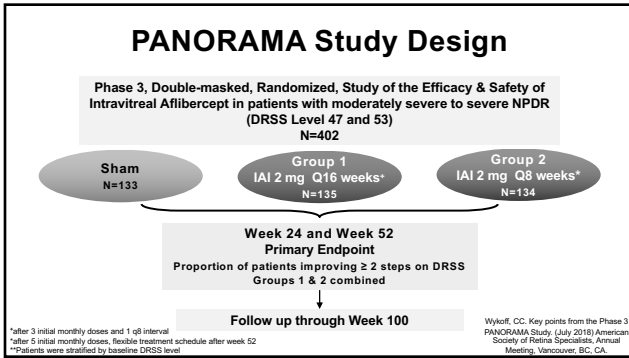
Pharmaceutical Dosing Can Improve DR Severity





Management of NPDR without DME

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- ### Inclusion & Exclusion Criteria
- **Inclusion**
 - Moderately severe to severe NPDR (DRSS levels 47 or 53), confirmed by the central reading center, in whom PRP could be safely deferred for 36 months
 - BCVA ETDRS letter score of ≥ 69 letters (~ Snellen equivalent of $\geq 20/40$)
 - **Exclusion**
 - Presence of DME threatening the center of the macula
 - Evidence of retinal neovascularization
 - Any prior treatment with:
 - Focal or grid laser photocoagulation or PRP
 - Systemic or intravitreal anti-VEGF agents
 - Intraocular steroids
 - Current ASNV, vitreous hemorrhage, or traction retinal detachment
 - HbA1c $>12\%$ or HbA1c $\leq 12\%$ with uncontrolled diabetes mellitus
 - Uncontrolled blood pressure
 - History of cerebrovascular accident or myocardial infarction within 6 months of study start
- Wykoff, CC. Key points from the Phase 3 PANORAMA Study (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

Dosing Schedule

Week:	BL	4	8	12	16	20	24	28	32	36	40	44	48	52	56	...100
SHAM*	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	...
Group 1*	X	X	X	O	X	O	X	O	X	O	X	O	X	O	X	...
Group 2*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	...

1 dose difference between Group 1 & 2 through week 24

+ Group 2 (Q8) group continues PRN through Week 100 based on DRSS level

*Patients progressing to PDR/ASNV or CI-DME were eligible for rescue treatment (IAI or laser) at the discretion of the investigator. Data for patients receiving rescue treatment was censored from the time of rescue.
X=active injection, O=sham injection

Wykoff, CC. Key points from the Phase 3 PANORAMA Study (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

Baseline Demographics

	Sham	Group 1	Group 2	All IAI	Total
N (FAS, SAF)	133	135	134	269	402
Age (years (SD))	55.8 (10.31)	55.4 (11.13)	55.8 (10.19)	55.6 (10.66)	55.7 (10.53)
Women # (%)	84 (48.1%)	60 (44.4%)	53 (39.6%)	113 (42.0%)	177 (44.0%)
Race # (%)					
White	107 (80.5%)	99 (73.3%)	104 (77.6%)	203 (75.5%)	310 (77.1%)
Black or African American	13 (9.8%)	16 (11.9%)	12 (9.0%)	28 (10.4%)	41 (10.2%)
Asian	4 (3.0%)	12 (8.9%)	7 (5.2%)	19 (7.1%)	23 (5.7%)
Other	9 (6.8%)	8 (5.9%)	11 (8.2%)	19 (7.1%)	28 (7.0%)
Hemoglobin A1C (%)	8.5 (1.54)	8.6 (1.69)	8.4 (1.64)	8.5 (1.66)	8.5 (1.62)
Duration of Diabetes (years (SD))	15.5 (9.34)	13.7 (8.61)	14.0 (9.69)	13.8 (9.15)	14.4 (9.24)
Diabetes Type 2	123 (92.5%)	121 (89.6%)	124 (92.5%)	245 (91.1%)	368 (91.5%)

Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8

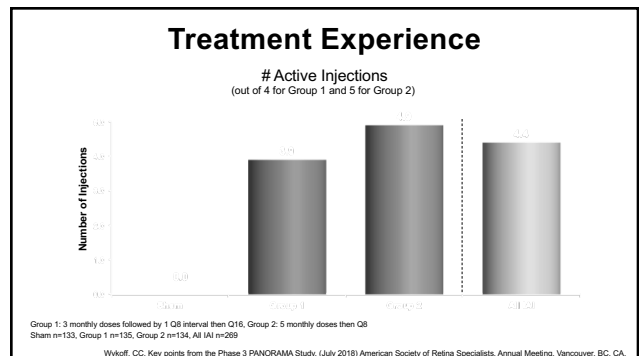
Wykoff, CC. Key points from the Phase 3 PANORAMA Study (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

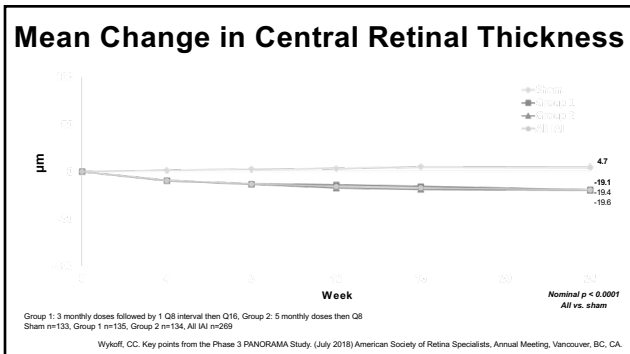
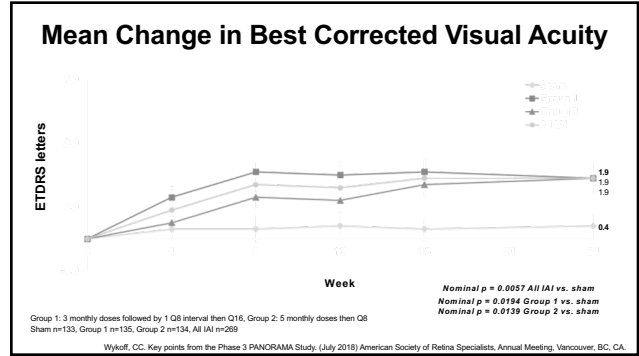
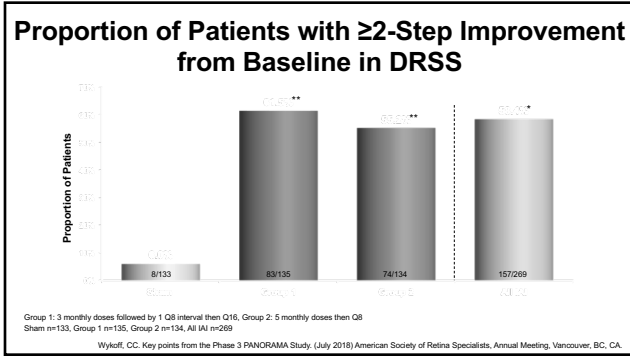
Baseline Disease Characteristics & Disposition

	Sham	Group 1	Group 2	All IAI	Total
N (FAS/SAF)	133	135	134	269	402
ETDRS BCVA (letters)	82.7 (6.03)	82.2 (6.63)	82.3 (5.15)	82.3 (5.93)	82.4 (5.96)
Mean (SD)	20/25	20/25	20/25	20/25	20/25
Snellen Equivalent	249.4	246.0	246.8	246.4	247.4
CRT (microns)	(38.41)	(34.34)	(31.59)	(32.94)	(34.82)
Mean (SD)					
Diabetic Retinopathy Severity Score (DRSS)					
Level 47	99 (74.4%)	102 (75.6%)	101 (75.4%)	203 (75.5%)	302 (75.1%)
Level 53	34 (25.6%)	33 (24.4%)	33 (24.6%)	66 (24.5%)	100 (24.9%)
Number of Patients who Completed at Week 24	119 (89.5%)	129 (95.6%)	132 (98.5%)	261 (97.0%)	380 (94.5%)

Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8

Wykoff, CC. Key points from the Phase 3 PANORAMA Study (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.



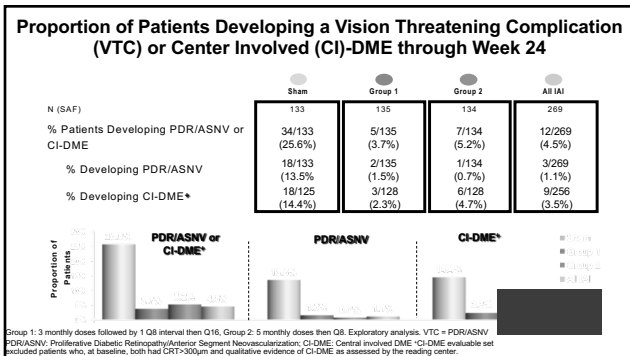


Safety Events Through Week 24

	Sham (n=133)	All IAI (n=269)
Ocular TEAEs (≥3%)		
Conjunctival hemorrhage	5 (3.8%)	32 (11.9%)
Vitreous floaters	1 (0.8%)	14 (5.2%)
Diabetic retinal edema	20 (15.0%)	11 (4.1%)
Eye pain	2 (1.5%)	11 (4.1%)
Diabetic retinopathy	4 (3.0%)	1 (0.4%)
Non Ocular Events		
Patients with ≥ 1 APTC, n (%)	2 (1.5%)	1 (0.4%)
Deaths	3 (2.3%)	0

- One Serious ocular AE of iris neovascularization occurred in 1 patient
- One ocular AE of vitreal cells occurred in 1 patient, which was considered mild

Wyckoff, CC. Key points from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.



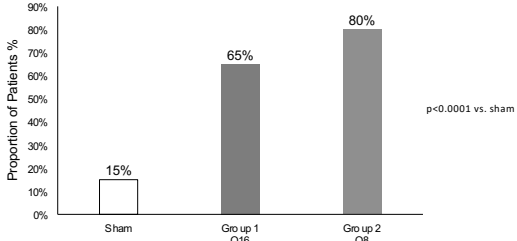
PANORAMA

Week 52 Outcomes

Proportion of Patients with ≥ 2 -Step Improvement from Baseline in DRSS

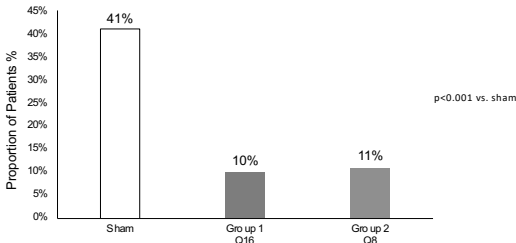
Atibbercept Improves Diabetic Retinopathy and Reduces Vision Threatening Complications in Phase 3 Trial; October 25, 2018. www.pmnswire.com

Proportion of Patients with ≥ 2 -Step Improvement from Baseline in DRSS



Atibbercept Improves Diabetic Retinopathy and Reduces Vision Threatening Complications in Phase 3 Trial; October 25, 2018. www.pmnswire.com

Proportion of Patients Developing a Vision Threatening Complication (VTC) or Center Involved (CI)-DME



Atibbercept Improves Diabetic Retinopathy and Reduces Vision Threatening Complications in Phase 3 Trial; October 25, 2018. www.pmnswire.com

**Front Line Diabetic Retinopathy
What Not to Miss and Why**

