Ranibizumab for Diabetic Macular Edema (DME)

Jason S. Ehrlich, MD, PhD

Associate Medical Director, Ophthalmology

Genentech, Inc., South San Francisco, CA

3/21/2012

Financial Disclosures & Personal Background

- I am an employee of Genentech, Inc., a member of the Roche Group, and my travel today was paid for by Genentech.
- As an employee, I also hold stock and/or stock options in Roche.
- I have no other financial disclosures.

- I am an ophthalmologist and the lead clinician and Medical Director for Genentech's studies of ranibizumab in diabetic macular edema.

- Prior to joining Genentech, I completed MD/PhD and Ophthalmology training at Stanford University School of Medicine. I was also a Clinical Instructor in Ophthalmology at Stanford and a Staff Physician at the VA Palo Alto Health Care System.

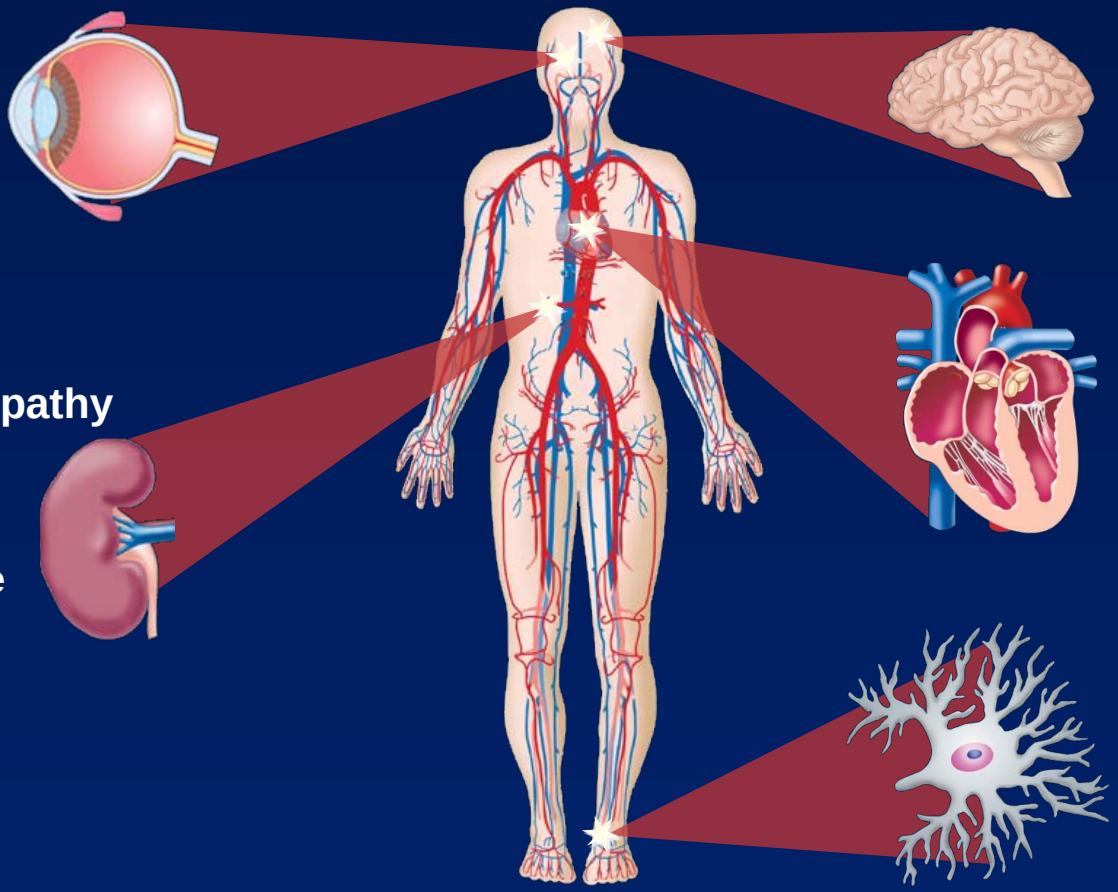
Type 2 Diabetes Is Associated with Serious Complications

Diabetic Retinopathy

Leading cause of new blindness in adults[1]

Diabetic Nephropathy

Leading cause of kidney failure/end-stage renal disease[1]



Stroke

2- to 4-fold increase in cardiovascular mortality and stroke[1]

Cardiovascular Disease

8/10 individuals with diabetes die from CV events[2]

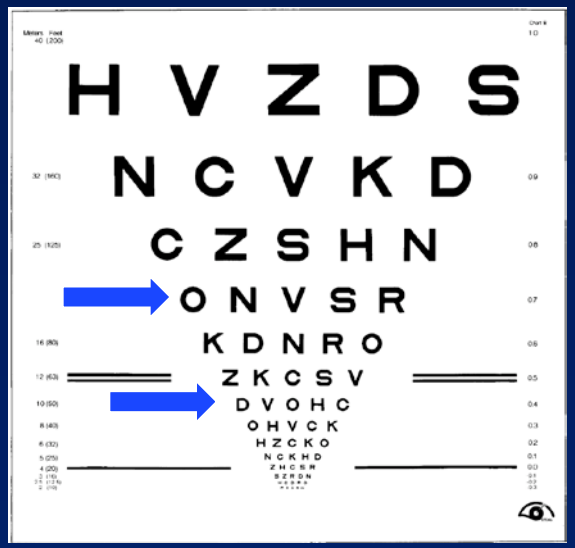
Diabetic Neuropathy

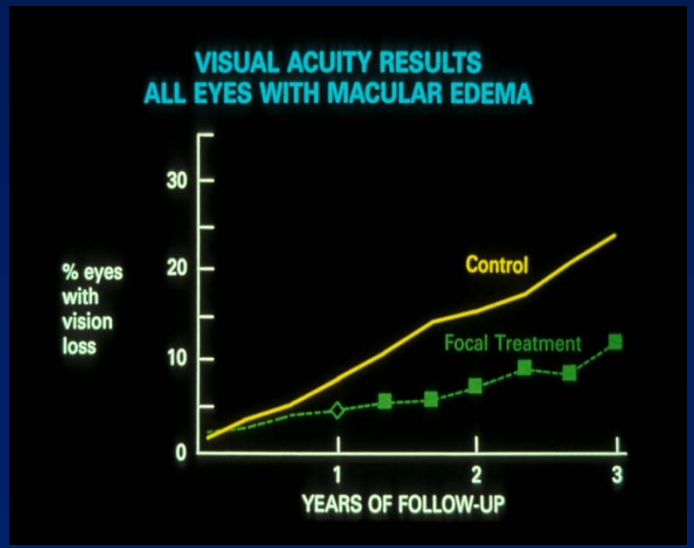
Leading cause of non-traumatic lower extremity amputations[1]

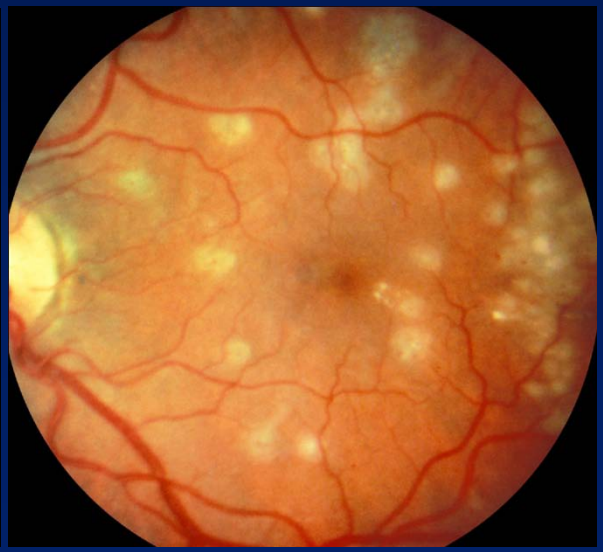
1. CDC Web site. National Diabetes Fact Sheet, 2011. Available at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed February 9, 2012.
2. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. *Endocr Pract.* 2007;13(suppl 1):4-69.

Macular Laser: Standard-Care Treatment for DME Since 1985

- Early Treatment of Diabetic Retinopathy Study (ETDRS)[1]
  - Showed macular laser photocoagulation effective for DME
  - Decreased risk of significant (3-line) visual acuity loss by 50%





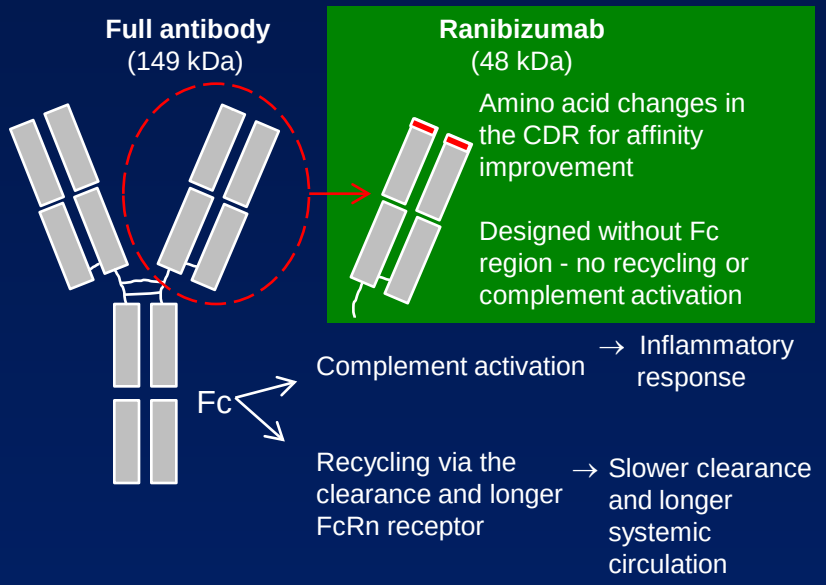


- Relatively few patients experience significant visual acuity improvement with laser, and improvements typically occur slowly
  - ~15% rate of 3-line improvement at 2 years in recent studies

1. ETDRS. *Arch Ophthalmol* 1985;103:1796–806.

Ranibizumab: Anti-VEGF Therapy Developed Specifically for Ophthalmic Use

- Ranibizumab is a humanized, monoclonal anti-VEGF Fab (antibody antigen binding fragment) specifically designed for use in the eye *(IND filed in 1999)*
- FDA-approved for other retinal vascular diseases:
  - Wet Age-Related Macular Degeneration (2006)
  - Macular Edema due to Retinal Vein Occlusion (2010)
- Not currently FDA-approved for DME
  - sBLA has been filed and is under review at FDA
  - If approved, will be only FDA-approved treatment for DME



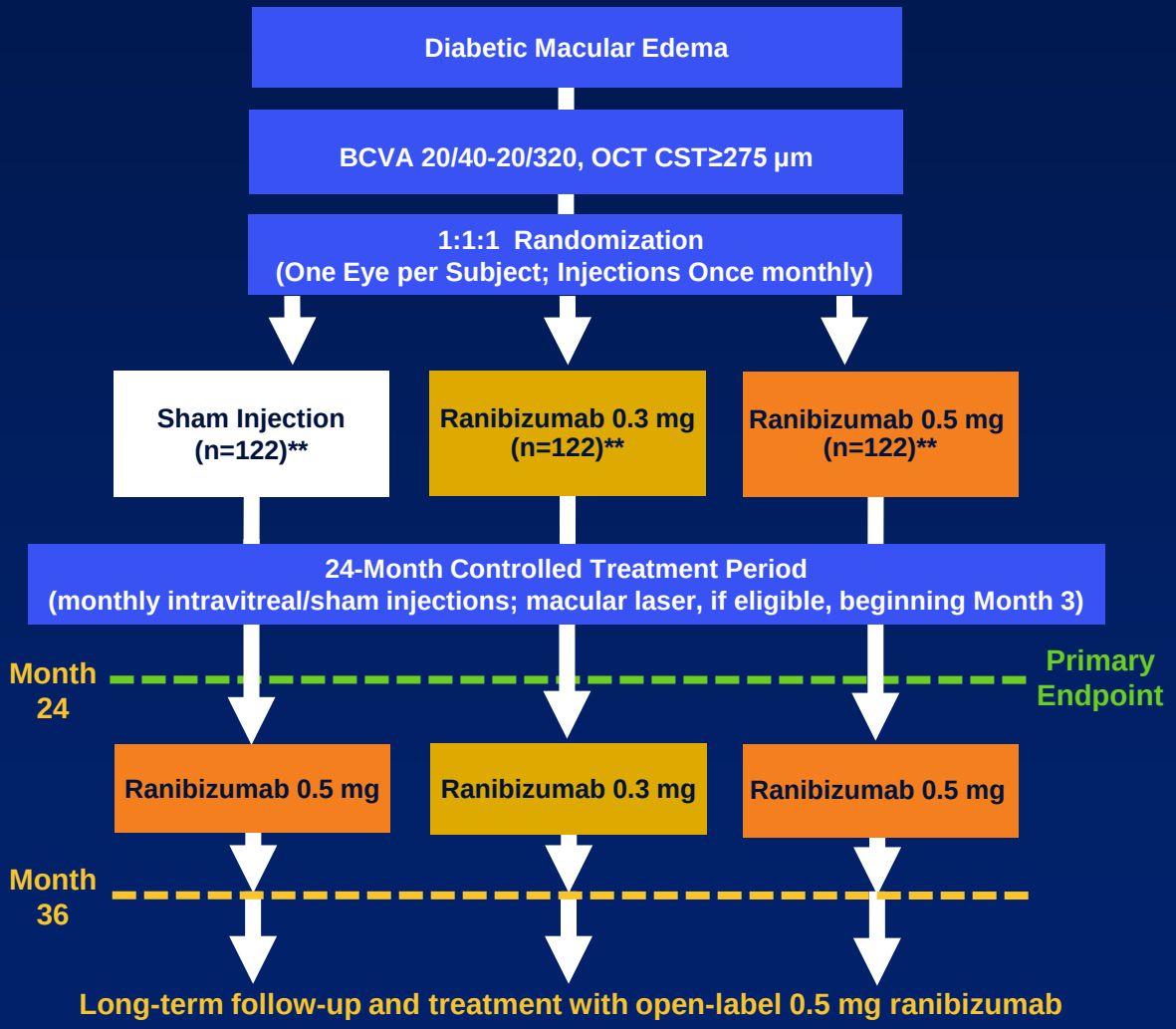
Desired Pharmacologic Attributes	Ranibizumab
Fully penetrates all retinal layers to reach target tissue	Low molecular weight; rapid, complete retinal penetration
Rapid systemic elimination	Serum elimination half life ~2 hours
Low potential for cell or complement mediated cytotoxicity	Designed without the Fc region of a full-length antibody
Binds and neutralizes VEGF-A with high affinity	High affinity binding (K_D<200pM) and potent neutralization of all known biologically active isoforms of VEGF-A

CDR = complementarity-determining regions; Fc = fragment crystallizable; FcRn = the neonatal Fc receptor for IgG; VEGF = vascular endothelial growth factor

Ferrara N et al. *Retina* 2006;26:859

Genentech Has Conducted Two RCTs for Ranibizumab in DME in Community-based Settings *(Question 6)*

- RIDE and RISE* are two Phase III studies evaluating the efficacy and safety of intravitreal ranibizumab, compared with sham injections, in patients with vision loss due to DME
- Both trials have good representation of important patient populations:
  - **≥65 years of age: 43.3%** (no significant differences in outcomes in subanalysis)
  - Hispanic ethnicity: 22.4%
  - Black or African-American race: 12.4%
- Both trials carried out in **community-based settings** (private practice and academic retina specialist offices)



RCT=randomized controlled trial

*Nguyen QD et al. *Ophthalmology* 2012. DOI #10.1016/j.ophtha.2011.12.039.

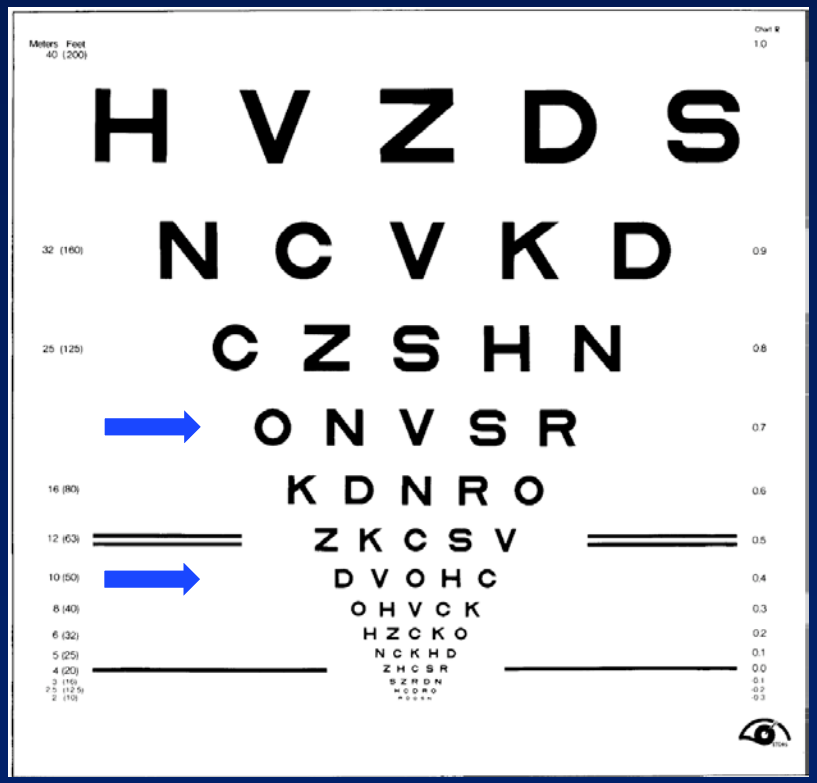
** Target Enrollment

Ranibizumab DME RCTs Included Common and Important Outcomes/Endpoints That Are Suitable to Assess DME *(Question 1)*

Outcome & Endpoint Measures	Benefit Seen with Ranibizumab in Phase III DME Studies
Visual Acuity: • % gaining ≥ 15 ETDRS letters • Mean BCVA (best-corrected visual acuity) change from baseline • % gaining ≥ 10 ETDRS letters • % losing < 15 ETDRS letters • % with Snellen equivalent 20/40 or better • Contrast sensitivity (Visual function measure not in Panel Questions)	✓
VFQ-25	✓
Dilated eye exam	✓
Grade of diabetic retinopathy	✓
Extent/progression as measured by retinal photography	✓
Fluorescein angiography	✓
Optical coherence tomography (OCT)	✓
Visual fields	Less Suitable in DME; Not Measured
Amsler grid	Less Suitable in DME; Not Measured

Visual Acuity Is a Common Outcome Measured by Ability to Read a Standardized Eye Chart

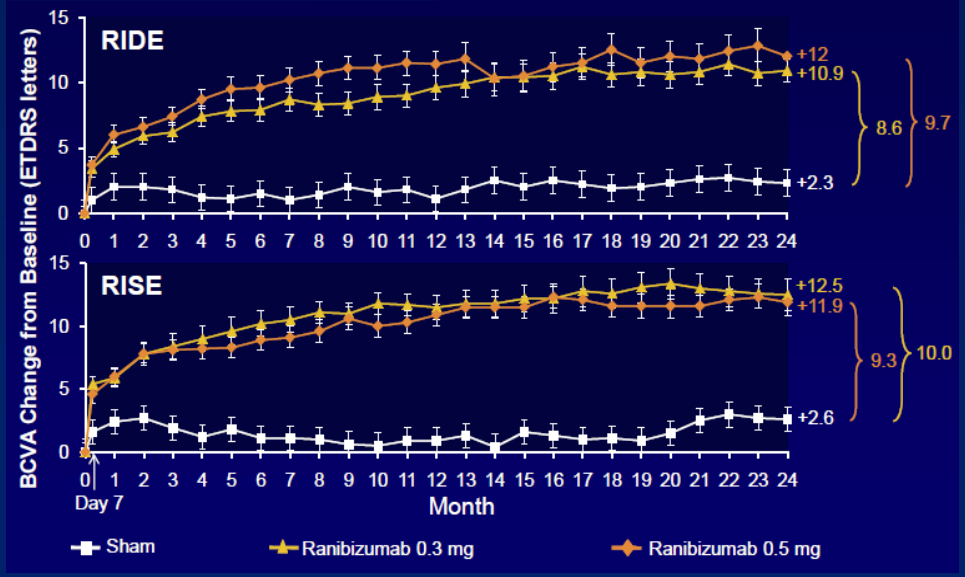
- Logarithmic, standardized eye chart improves statistical comparisons for ophthalmology clinical trials
- More letters read = better visual acuity (VA)
- Delta of:
  - 15 letters = 3 lines
  - 10 letters = 2 lines
  - 5 letters = 1 line



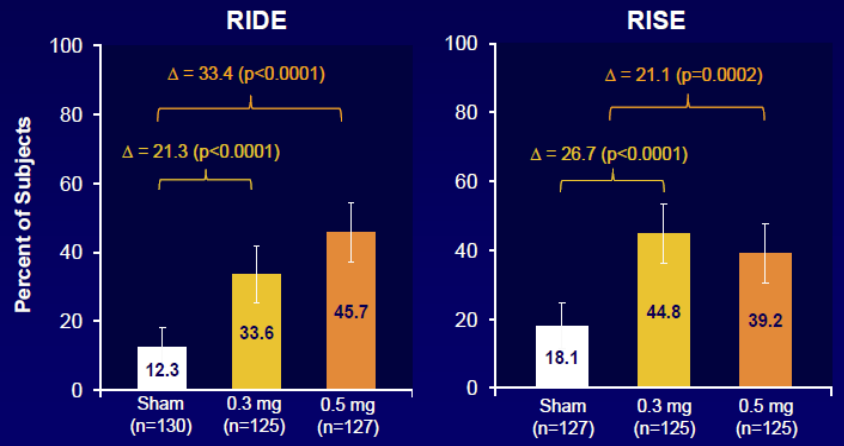
Ranibizumab Treatment Leads to Clinically Meaningful Improvements in Visual Acuity in DME *(Question 2/3)*

- Ranibizumab treatment resulted in rapid and sustained improvement in both vision and retinal anatomy
  - Statistically significant visual acuity improvements and reductions in macular edema observed at 7 days after first treatment, and subsequently improved over 24 months

Mean Change in BCVA From Baseline Over Time



Subjects Gaining ≥15 ETDRS Letters from Baseline at Month 24



*Nguyen QD et al. *Ophthalmology* 2012. DOI #10.1016/j.ophtha.2011.12.039.

Patient Reported Outcomes in RIDE and RISE Were Measured Using the National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

- Questionnaire administered by trained interviewer that captures patient perception of impact of vision problems on function
- 25 questions, 11 subscales plus general health rating question
  - Near Activities* (EX: reading ordinary print in newspaper, finding objects on a crowded shelf)
  - Distance Activities* (EX: going down the stairs in dim light or at night, viewing television programs)
  - Vision-specific Dependency*
  - Vision-Specific Social Functioning
  - Vision-Specific Mental Health
  - Vision-Specific Role Difficulties
  - Driving
  - Ocular Pain
  - Color Vision
  - Peripheral Vision
  - General Vision
  - General Health
- Scores 0 (worst) - 100 (perfect visual function)
  - Clinically Meaningful Change
    - 5 point change in VFQ score correlated with 15-letter VA change

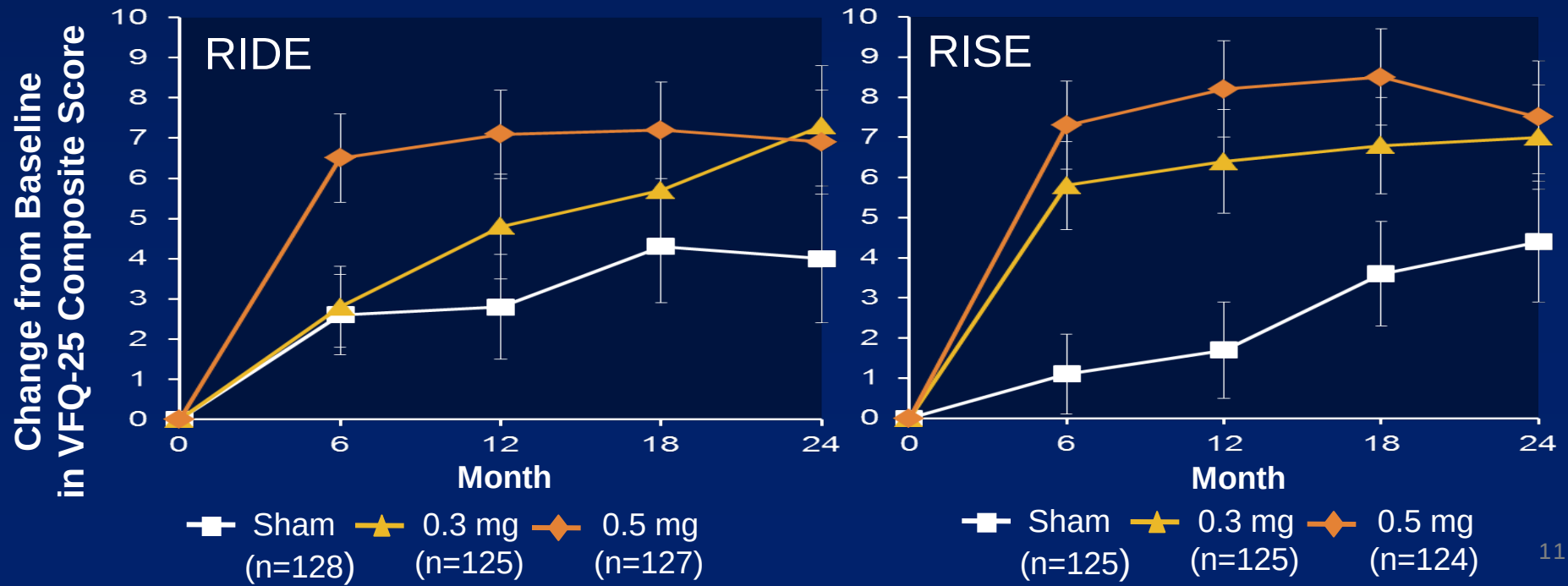
*Prespecified as a secondary efficacy endpoint in the RIDE and RISE trials

Ranibizumab Improves DME Patient-Reported Outcomes on Visual Function Questionnaire (VFQ-25) *(Question 2/3)*

Reading ordinary print in newspapers

Seeing and enjoying programs on TV

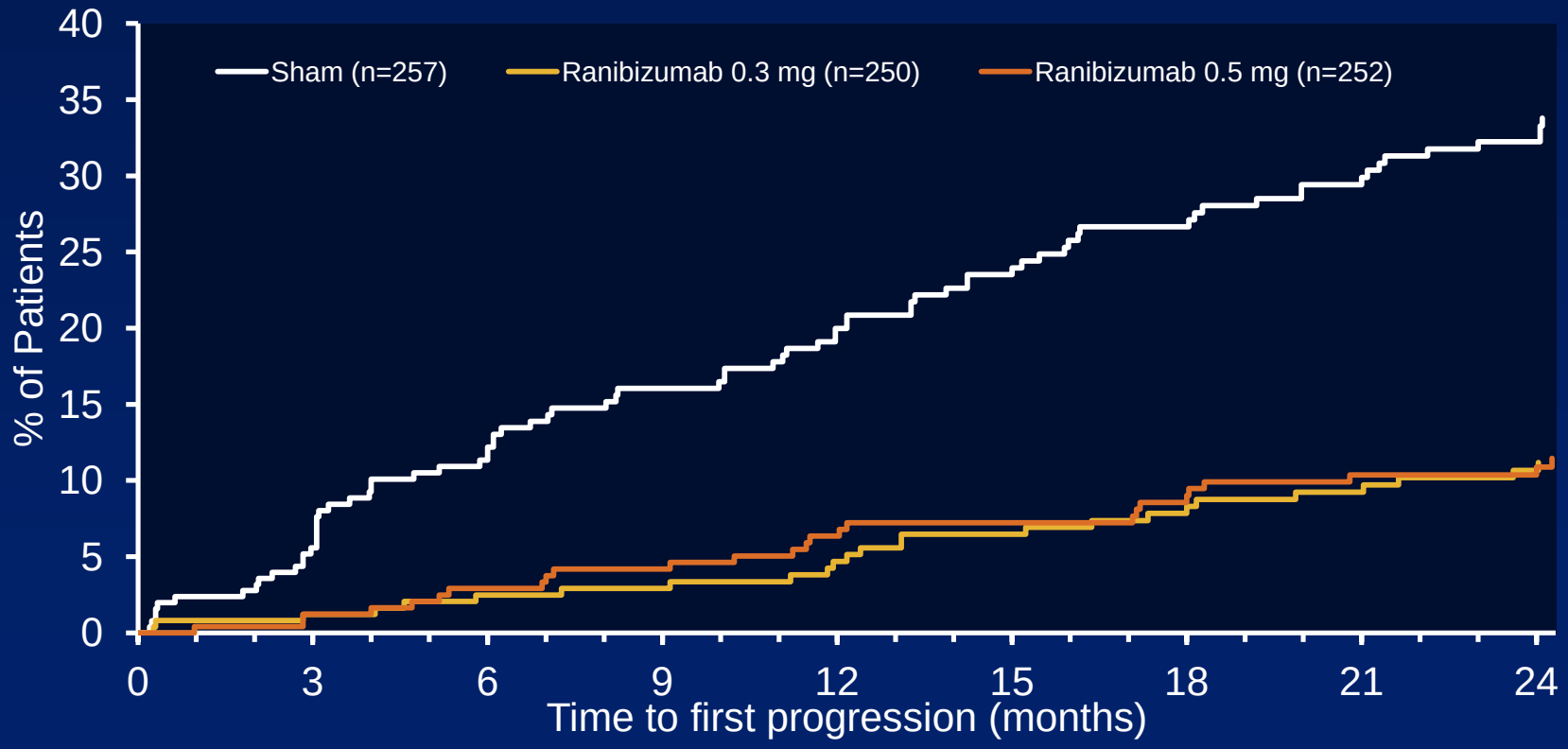
Finding objects on a crowded shelf



Ranibizumab Significantly Slows Progression to Proliferative Diabetic Retinopathy *(Question 2/3)*

Time to Development of Proliferative Diabetic Retinopathy

(Post Hoc Analysis)



Progression defined as any of: Change from NPDR to PDR on color fundus photos, Administration of panretinal photocoagulation, Cases identified by opthalmoscopy, Vitrectomy surgery performed for DR-related reasons, Occurrence of vitreous hemorrhage or adverse events of iris NV or retinal NV

Low Overall Rates of Serious Adverse Events in RIDE & RISE Clinical Trials

(Note: Table includes selected events; complete information in appendix)

- **Ocular safety consistent with Phase III studies of ranibizumab in non-DME patients**
  - Fewer ocular events related to diabetic retinopathy with ranibizumab compared to sham
- **Low rates of events potentially related to systemic VEGF inhibition**
  - Strokes and overall mortality were numerically slightly higher with monthly 0.5 mg ranibizumab
  - Higher rates of stroke and death were not seen in two other large, non-Genentech sponsored studies of 0.5 mg ranibizumab in DME, although patients received less than monthly dosing in those studies

Selected Category / Event , n (%) MedDRA High Level Term or Preferred Term	**Sham** **(n=250)**	**Ranibizumab** **0.3 mg** **(n=250)**	 **0.5 mg** **(n=250)**
Any Ocular Serious Adverse Event (SAE)	**16 (6.4)**	**8 (3.2)**	**19 (7.6)**
Cataract Traumatic	0	1 (0.4)	2 (0.8)
Endophthalmitis	0	2 (0.8)	2 (0.8)
Vitreous Haemorrhage	7 (2.8)	0	2 (0.8)
Any Systemic SAE Potentially Related to VEGF Inhibition	**25 (10.0)**	**19 (7.6)**	**22 (8.8)**
Arterial Thromboembolic Events	20 (8.0)	13 (5.2)	16 (6.4)
Myocardial Infarction*	9 (3.6)	9 (3.6)	7 (2.8)
CVA+	4 (1.6)	3 (1.2)	8 (3.2)†
Transient Ischaemic Attack	5 (2.0)	1 (0.4)	1 (0.4)
Deaths, Overall	3 (1.2)	7 (2.8)	11 (4.4)
Vascular death	3 (1.2)	5 (2.0)	6 (2.4)
Unknown cause	0	0	1 (0.4)†

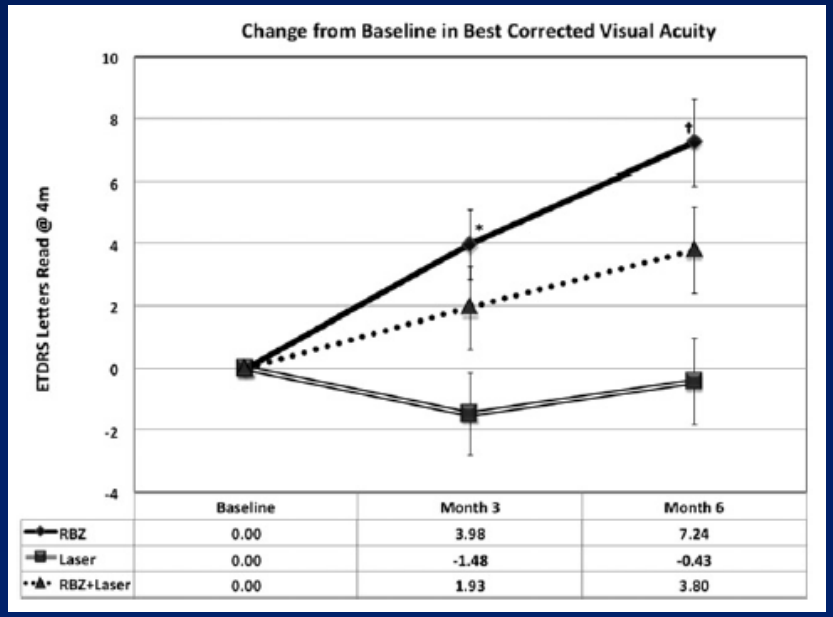
* MedDRA = Medical Dictionary for Regulatory Activities, Version 13.1, * Myocardial infarction includes preferred terms of acute myocardial infarction and myocardial infraction.
† Includes one subject assigned to sham who had a stroke (2008), received a single dose of 0.5mg RBZ in error (2009), and died of unknown cause (2010).
+ CVA = cerebrovascular accident, includes preferred terms of cerebrovascular accident, ischaemic stroke, and lacunar infarction.

Phase II RCTs Provided Early Evidence that Ranibizumab Improves Outcomes vs. Other DME Management *(Question 2/3)*

- **READ-2:** Investigator-Sponsored Trial (Genentech-supported; n=126; U.S.)
  - Significantly greater mean change in the VA in ranibizumab group versus laser group

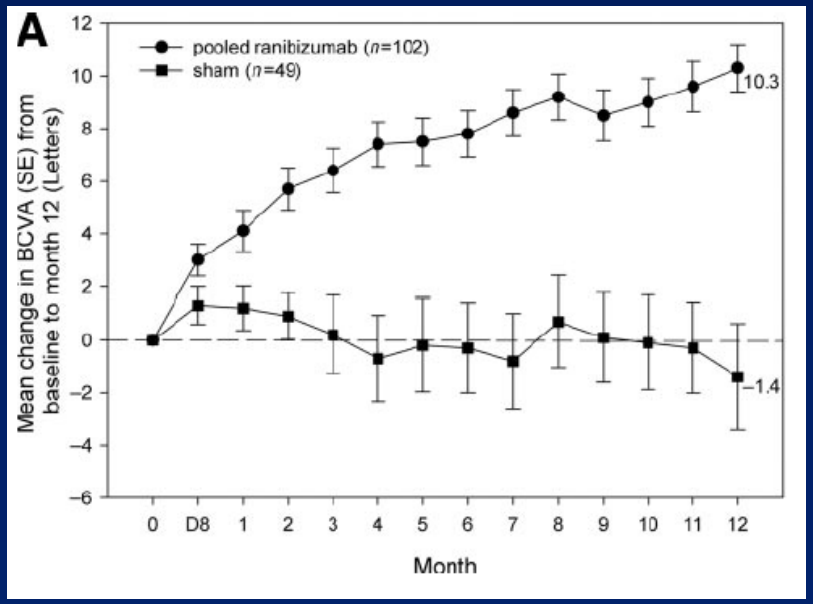
- **RESOLVE:** Novartis Phase II RCT (n=151; ex-U.S.)
  - Significantly greater average improvements in vision in ranibizumab-treated patients versus sham

READ-2



READ-2: 0.5 mg ranibizumab alone, 0.5 mg ranibizumab + laser, laser alone
Nguyen QD et al. *Ophthalmology* 2009:116;2175-2181

RESOLVE



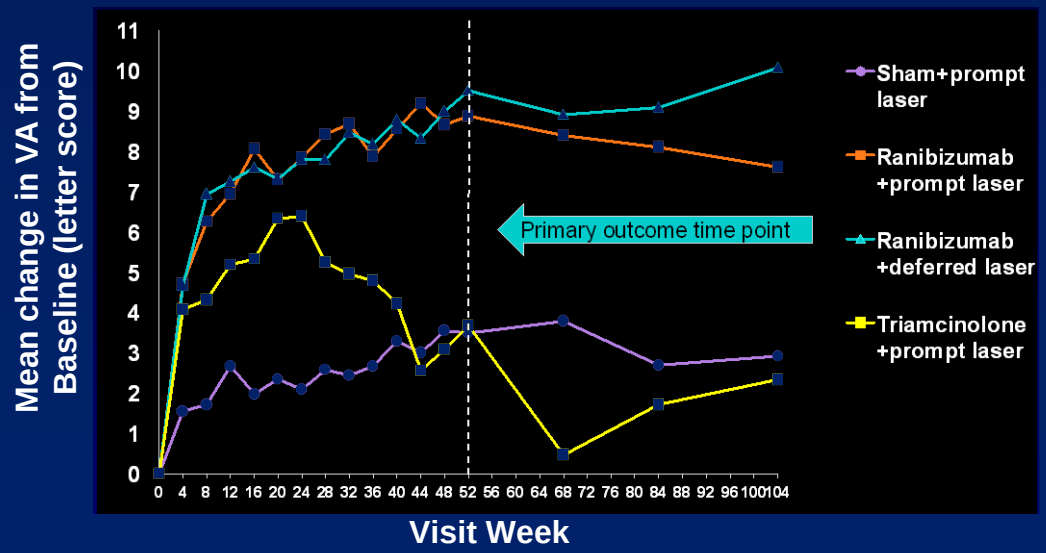
RESOLVE: 0.3 mg ranibizumab, 0.5 mg ranibizumab, sham injection (laser per rescue criteria for all groups)
Massin P et al. *Diabetes Care* 2010:33;2399-2405

Additional Phase III RCTs also Show Ranibizumab Improves Outcomes, Compared to Other DME Management *(Question 2/3)*

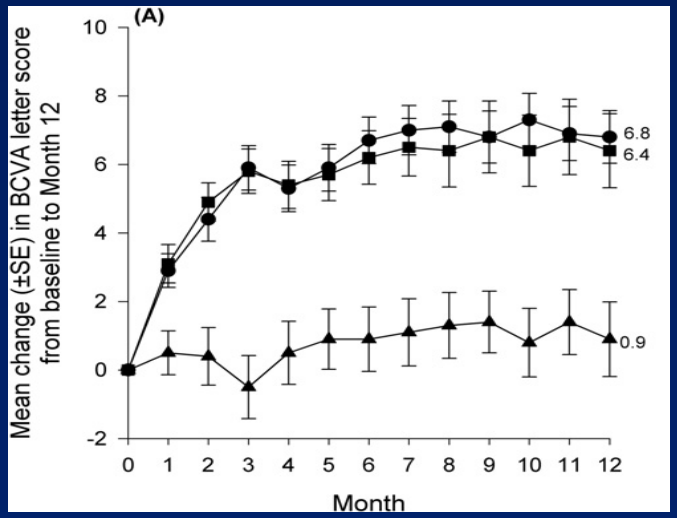
- **DRCR.net:** NEI Phase III RCT (n=691; U.S.)
  - Significantly greater mean change in the VA in ranibizumab groups versus laser groups

- **RESTORE:** Novartis Phase III RCT (n=345; ex-U.S.)
  - Significantly greater average improvements in vision in ranibizumab-treated patients versus laser
  - Greater improvements in patient-reported visual outcomes in ranibizumab patients (NEI VFQ-25); *results in appendix*

DRCR.net



RESTORE



DRCR.net: Sham+Macular laser, triamcinolone+laser, 0.5 mg ranibizumab+prompt laser, 0.5 mg ranibizumab+deferred laser
Elman MJ et al. *Ophthalmology* 2010;117:1064-77 e35

RESTORE: Macular laser, 0.5 mg ranibizumab alone, 0.5 mg ranibizumab/ laser
Mitchell P et al. *Ophthalmology* 2011;118:615–625.

No Level 1* Evidence Exists Comparing Health Outcomes of Various Anti-VEGFs in DME *(Question 4/5)*

- Genentech is not aware of any level 1* evidence comparing health outcomes of various intravitreal anti-VEGF treatments for DME
- While there are noncomparative studies available on individual anti-VEGF therapies used in DME, these studies may lack one or more of the following key study design features, making indirect treatment comparisons (ITCs) between these studies and RIDE/RISE difficult:

RIDE/RISE Key Study Design Aspects	Importance
Sufficient number of patients with characteristics similar to Medicare beneficiaries: • Age and other demographics • Medications/diabetes treatment goals (vary geographically)	Ensures results relevant to Medicare population
Prospective, randomized, double-masked, multicenter trial, with sufficient number of patients	Minimize bias and variability
Standardization of data collection: • ETDRS visual acuity collection protocol • Independent evaluation of imaging data	Minimize bias and variability
Appropriate data analysis • Statistical methods and Type 1 error control described	Minimize bias
Length of treatment period sufficient	Short term outcomes may not always predict long term outcomes

- Differences in baseline visual acuity make cross-trial comparisons difficult due to floor and ceiling effects

*Level 1 evidence defined as, “Evidence obtained from at least 1 properly designed randomized controlled trial.” US Department of Health and Human Services. US Preventive Task Force: Agency for Healthcare Research and Quality. Available at: http://www.ahrq.gov/CLINIC/uspstfix.htm. Accessed October 17, 2009.

No Level 1* Evidence Exists Comparing Health Outcomes of Various Anti-VEGFs in DME *(Question 4/5)*

- Genentech is not aware of any level 1[1] evidence comparing health outcomes of various intravitreal anti-VEGF treatments for DME
- Level 1 evidence does exist comparing anti-VEGFs for wet AMD, but DME and wet AMD patients differ substantially
  - The National Eye Institute-sponsored Comparison of Age-related Macular Degeneration Treatment Trials (CATT)[2] comparing bevacizumab and ranibizumab only studied wet AMD patients, not DME patients
    - Unlike bevacizumab, ranibizumab was specifically designed, formally studied, approved by the FDA[3], & manufactured for intraocular delivery
  - Similarly, data from Level 1 studies comparing aflibercept and ranibizumab[4] are available only in wet AMD, but not in DME

[1]Level 1 evidence defined as, "Evidence obtained from at least 1 properly designed randomized controlled trial." US Department of Health and Human Services. US Preventive Task Force: Agency for Healthcare Research and Quality. Available at: http://www.ahrq.gov/CLINIC/uspstfix.htm. Accessed October 17, 2009.
[2] CATT Research Group et al. *N Engl J Med*. 2011; 364:1897-1908.
[3] FDA approved for wet AMD (2006) and macular edema due to retinal vein occlusion (2010)
[4] EYLEA™ [package insert]. Regeneron Pharmaceuticals, Inc.; Tarrytown, NY. November, 2011.

DME and Wet AMD Patients Differ Substantially

Characteristic	DME Patients	Wet AMD Patients
Visual Disease Pathophysiology	• Microvascular Complication of Long-Standing Diabetes	• Complication of Macular Degeneration
Demographics	• Generally Younger • Diverse Races/Ethnicities	• Generally Older • Typically Caucasian

Medical Co-Morbidities	• Typically related to underlying diabetes:
	  • Cardiovascular Disease
	  • Nephropathy
	  • Neuropathy
	• Often higher cardiovascular risk than both general population and DM patients without advanced retinopathy
		• Typical diseases of the elderly

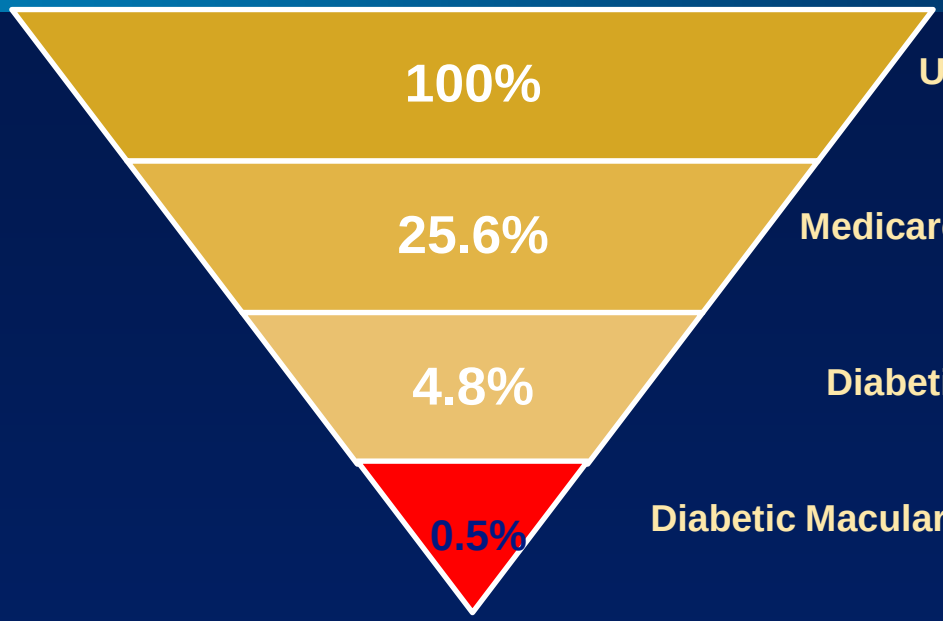
Overall Conclusions

- There is robust evidence, from multiple studies, to conclude that DME management using intravitreal ranibizumab improves patient health outcomes, compared to DME management without ranibizumab
- The outcomes are broadly applicable to patients with DME, including Medicare beneficiaries and patients in community-based settings
- While not currently FDA-approved as a treatment for DME (under review at FDA), ranibizumab demonstrated significant benefit in multiple clinical trials for a serious disease that severely impacts patients' health and quality of life
- Importantly, these results underscore the need for appropriate treatment of DME patients


Genentech
A Member of the Roche Group

APPENDIX

DME Population Represents A Very Small Percent of Medicare-Eligible Patients*



Prevalence of DR in Subpopulations (NHIS 2002 Data)[2]

Latinos

- 9.3% of Latinos diagnosed with diabetes (19.2 M)
  - Of those, 1.3% had diabetic retinopathy

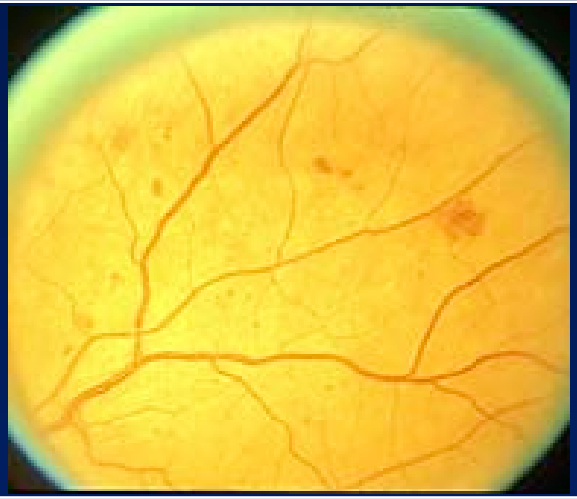
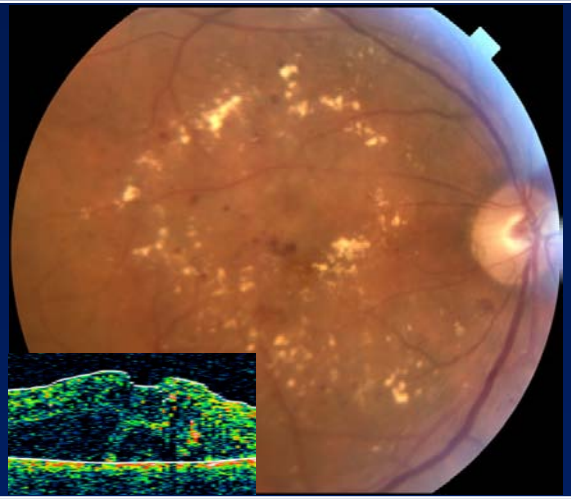
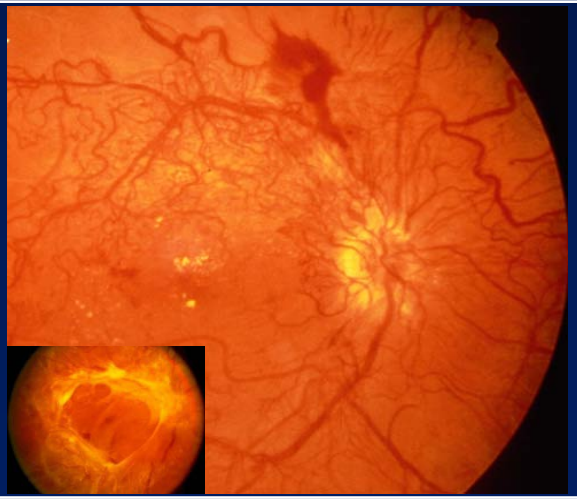
African Americans

- 10.1% of Non-Hispanic Blacks diagnosed with diabetes
  - Of those, 1.2% had diabetic retinopathy

*Prevalence

1. Lee PP et al. Longitudinal prevalence of major eye diseases. *Arch Ophthalmol*. 2003 Sep;121(9):1303-10.
2. Ryskulova A et al. *AJPH* 2008:454-461

Spectrum of Diabetic Retinopathy Severity

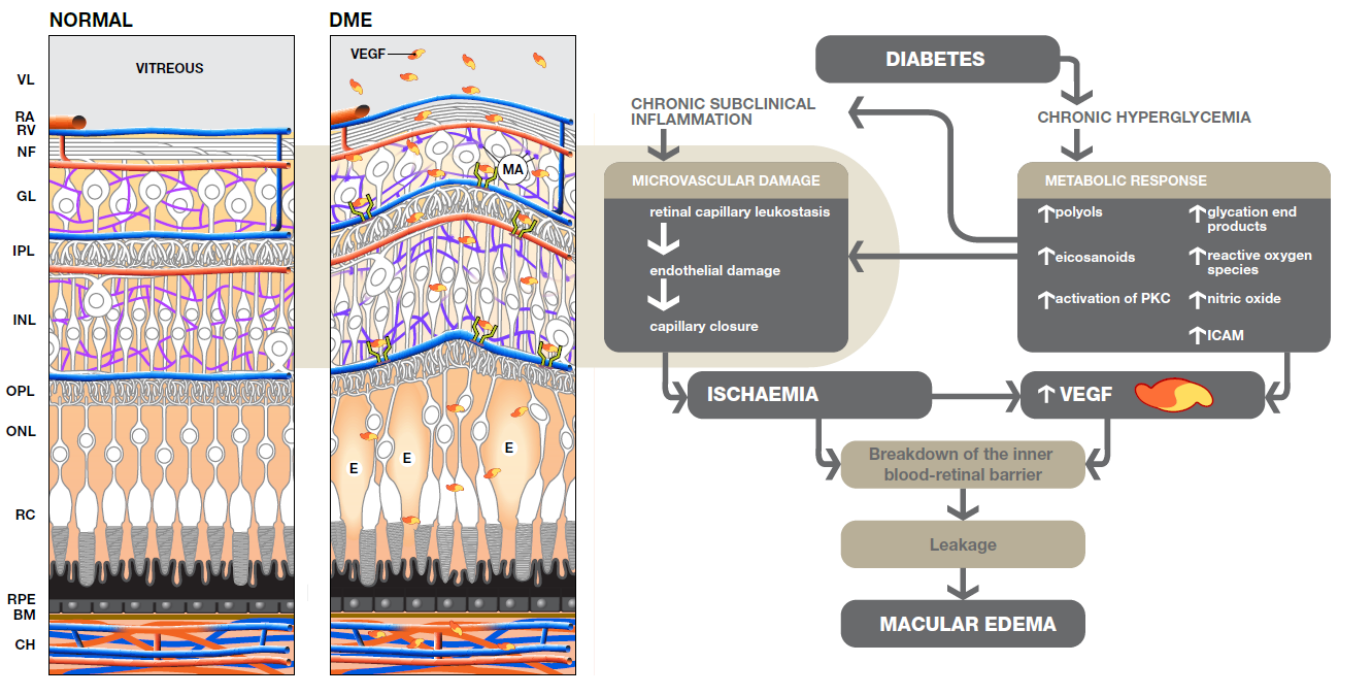
Non-Proliferative DR	Diabetic Macular Edema	Proliferative DR
		
Microvascular damage	**Swelling in central retina**	**End stage**
• Chronic, occurring over years • Typically no significant vision loss, but progresses to DME and/or PDR • Similar damage occurs in other end-organ vascular beds	• ***Accounts for most vision loss*** • Co-exists with NPDR and PDR	• Neovascularization of retina • High risk of severe visual loss

More common
Less severe

Less common
More severe

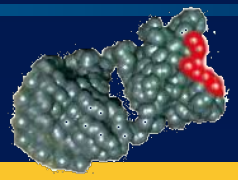
Rationale for Anti-VEGF Therapy in DME

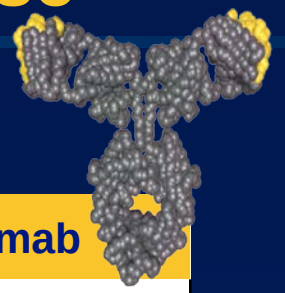
- Vascular leakage and proliferation in DR may be controlled by blockade of vascular endothelial growth factor A (VEGF):
  1. Vascular hyperpermeability and angiogenesis are key responses elicited by VEGF[1]
  2. VEGF is implicated in blood-retinal barrier breakdown in DME[2]
  3. Intraocular levels of VEGF are increased in DME[3]



1. Ferrara N et al. *Retina* 2006;26:859.
2. Antonetti DA et al. *JBC*. 1999;274:23463
3. Funatsu H et al. *Am J Ophthalmol* 2002;133:70–7.

Ranibizumab: Anti-VEGF Therapy Developed Specifically for Ophthalmic Use





	Ranibizumab	Bevacizumab
Molecular Structure	Antibody fragment (Fab)	Full-length Antibody
Fc region*	Absent	Present
Molecular Mass	48 kD	149 kD
Cell Type for Production†	E. coli	Chinese Hamster Ovary cells
Affinity Maturation‡	100-fold increase§	None
Binding Affinity to VEGF-A (per Molar)	5 to 20-fold	1-fold
Vitreous Elimination Half-Life (in humans)	9 Days	Unknown
Systemic Elimination Half-Life (in humans)	Hours‖	Weeks¶
Manufactured to meet specifications for drugs administered into the eye	Yes	No

Notes: * Fc portion has the potential to cause inflammation and prolong half-life of the antibody; †Glycosylation, a post-translational modification to proteins, occurs in proteins produced in a eukaryotic cell line, such as CHO cells. Glycosylation of a protein stabilizes the protein from systemic enzyme degradation; ‡Affinity maturation is a process involving modification of amino acid sequence to improve the affinity of a protein molecule; §Compared with Fab-12, a humanized Fab variant which bevacizumab was derived from; ‖In the absence of human pharmacokinetic data following intravenous administration, the intrinsic systemic elimination half-life of ranibizumab was estimated to be 0.09 days (2 hours) based on the assumption that humans share similar characteristics seen in animal models; ¶As stated in the prescribing information, based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11-50 days).
Abbreviation: Fab= antibody fragment; kD=kilodalton; VEGF-A= vascular endothelial growth factor A.

Note: Figures provided for illustrative purposes

Avastin® [package insert]. Genentech; South San Francisco, CA. Data on file (14624); Data on file (14625); Ferrara N et al. *Retina* 2006;26:859-870.; Lucentis® [package insert]. Genentech; South San Francisco, CA. Mimura Y et al. Biochem Soc Trans 2000;28. Abstract #A256.; Yet M et al. Abstr Am Chem Soc 1992;203. ACS Abstract #BIOT55.

The RIDE and RISE Studies Address Many Commonly Used Endpoint Measures *(Question 2/3)*

Yellow = measure noted in MEDCAC key panel question Endpoint at Month 24	RIDE			RISE		
		Ranibizumab			Ranibizumab	
	Sham (n=130)	0.3 mg (n=125)	0.5 mg (n=127)	Sham (n=127)	0.3 mg (n=125)	0.5 mg (n=125)
≥ 15 letters gained from baseline, % (95% CI)	**12.3 (6.7-18.0)**	**33.6 (25.3-41.9)**	**45.7 (37.0—54.3)**	**18.1 (11.4-24.8)**	**44.8 (36.1-53.5)**	**39.2 (30.6-47.8)**
Mean BCVA change from baseline, letters (SD)	**2.3 (14.2)**	**10.9 (10.4)**	**12.0 (14.9)**	**2.6 (13.9)**	**12.5 (14.1)**	**11.9 (12.4)**
≥ 10 letters gained from baseline, % (95% CI)	25.4 (17.9-32.9)	59.2 (50.6-67.8)	64.6 (56.2-72.9)	29.9 (22.0-37.9)	62.4 (53.9-70.9)	62.2 (53.9-70.9)
Snellen equiv. 20/40 or better, % (95% CI)	34.6 (26.4-42.8)	54.4 (45.7-63.1)	62.2 (53.8-70.6)	37.8 (29.4-46.2)	60.0 (51.4-68.6)	63.2 (54.7-71.7)
< 15 letters loss from baseline, % (95% CI)	91.5 (86.8-96.3)	98.4 (96.2-100)	96.1 (92.7-99.4)	89.8 (84.5-95.0)	97.6 (94.9-100)	97.6 (94.9-100)
Mean OCT CFT change, µm (SD)	**-125.8 (198.3)**	**-259.8 (169.3)**	**-270.7 (201.6)**	**-133.4 (209.0)**	**-250.6 (212.2)**	**-253.1 (183.7)**
OCT CFT ≤ 250 µm, % (95% CI)	**46.2 (37.6-54.7)**	**76.0 (68.5-83.5)**	**81.1 (74.3-87.9)**	**43.3 (34.7-51.9)**	**74.4 (66.7-82.1)**	**76.0 (68.5-83.5)**
≥ 3 step worsening of ETDRS DR severity, % (95% CI)	5.6 (1.6-9.7)	1.7 (0-4.1)	0	4.3 (0.6-8.1)	0.9 (0-2.5)	1.7 (0-4.1)
resolution of leakage on FA, % (95% CI)	**2.3 (0-4.9)**	**17.1 (10.4-23.7)**	**30.7 (22.7-38.7)**	**1.6 (0-3.8)**	**30.1 (22.0-38.2)**	**26.0 (18.3-33.8)**
receiving ≥1 macular laser treatment, % (95% CI)	70.0 (62.1-77.9)	36.0 (27.6-44.4)	19.7 (12.8-26.6)	74.0 (66.4-81.6)	39.2 (30.6-47.8)	35.2 (26.8-43.6)
VFQ-25 Composite Score, mean change from baseline (SD)	4.0 (17.6)	7.3 (16.2)	6.9 (14.2)	4.4 (16.3)	7.0 (14.9)	7.5 (15.7)

Patient Eligibility Criteria for RIDE and RISE

- **Key inclusion criteria:***
  - Adults (≥18 years) with decrease in vision due primarily to DME
  - Center subfield thickness (CST) ≥275 µm
  - Study eye Best Corrected Visual Acuity (BCVA) of 20/40 to 20/320†
- **Key exclusion criteria:***
  - History of any of the following within 3 months prior to Day 0:
    - Anti-angiogenic drugs in either eye
    - Pan-retinal photocoagulation (PRP), macular laser, intraocular steroids or surgery in the study eye
    - Cerebral vascular accident (CVA) or myocardial infarction (MI)
  - Active proliferative diabetic retinopathy or uncontrolled glaucoma in the study eye
  - Glycosylated hemoglobin (HbA1c) >12%

*A complete list of the eligibility criteria is posted on www.clinicaltrials.gov.
†Approximate Snellen equivalent.

Subject Demographic and Baseline Characteristics for RIDE and RISE

Characteristic	RIDE			RISE		
		Ranibizumab			Ranibizumab	
	Sham (n=130)	0.3 mg (n=125)	0.5 mg (n=127)	Sham (n=127)	0.3 mg (n=125)	0.5 mg (n=125)
Demographic characteristics						
Age (y), mean (SD)	63.5 (10.8)	62.7(11.1)	61.8 (10.1)	61.8 (9.8)	61.7 (8.9)	62.8 (10.0)
Male, n (%)	66 (50.8)	73 (58.4)	80 (63.0)	74 (58.3)	73 (58.4)	65 (52.0)
Race, n (%)*						
Black or African American	15 (11.5)	14 (11.2)	13 (10.2)	19 (15.0)	18 (14.4)	14 (11.2)
White	104 (80.0)	99 (79.2)	105 (82.7)	101 (79.5)	97 (77.6)	97 (77.6)
Hispanic or Latino, n (%)	37 (28.5)	33 (26.4)	31 (24.4)	24 (18.9)	20 (16.0)	25 (20.0)
Diabetes status at baseline						
Duration (y), mean (SD)†	16.6 (10.6)	16.0 (9.8)	15.3 (10.1)	14.5 (9.9)	15.9 (9.9)	16.3 (8.5)
Mean HbA1c, % (SD)¶	7.6 (1.4)	7.6 (1.3)	7.6 (1.5)	7.7 (1.5)	7.7 (1.5)	7.7 (1.4)

* Subjects who are of more than one race were counted for each category that they indicated.
†At randomization; sham/0.3mg/0.5mg: RIDE (n=122/119/124), RISE (n=123/118/118).
¶ Sham/0.3mg/0.5mg: RIDE (n=125/120/123), RISE (n= 123/120/120). + Sham/0.3mg/0.5mg: RIDE (n=128/125/127), RISE (n=125/125/124)
HbA1c = glycosylated hemoglobin; SD = standard deviation.

Macular and Panretinal Laser Use in RIDE and RISE

	RIDE			RISE		
		Ranibizumab			Ranibizumab	
	Sham (n=130)	0.3 mg (n=125)	0.5 mg (n=127)	Sham (n=127)	0.3 mg (n=125)	0.5 mg (n=125)
Macular focal/grid laser treatment during study						
Received macular laser, n (%)*	91 (70.0)	45 (36.0)	25 (19.7)	94 (74.0)	49 (39.2)	44 (35.2)
Panretinal photocoagulation (PRP) laser treatment during study						
Received PRP, n (%)	16 (12.3)	2 (1.6)	2 (1.6)	14 (11.0)	0	1 (0.8)

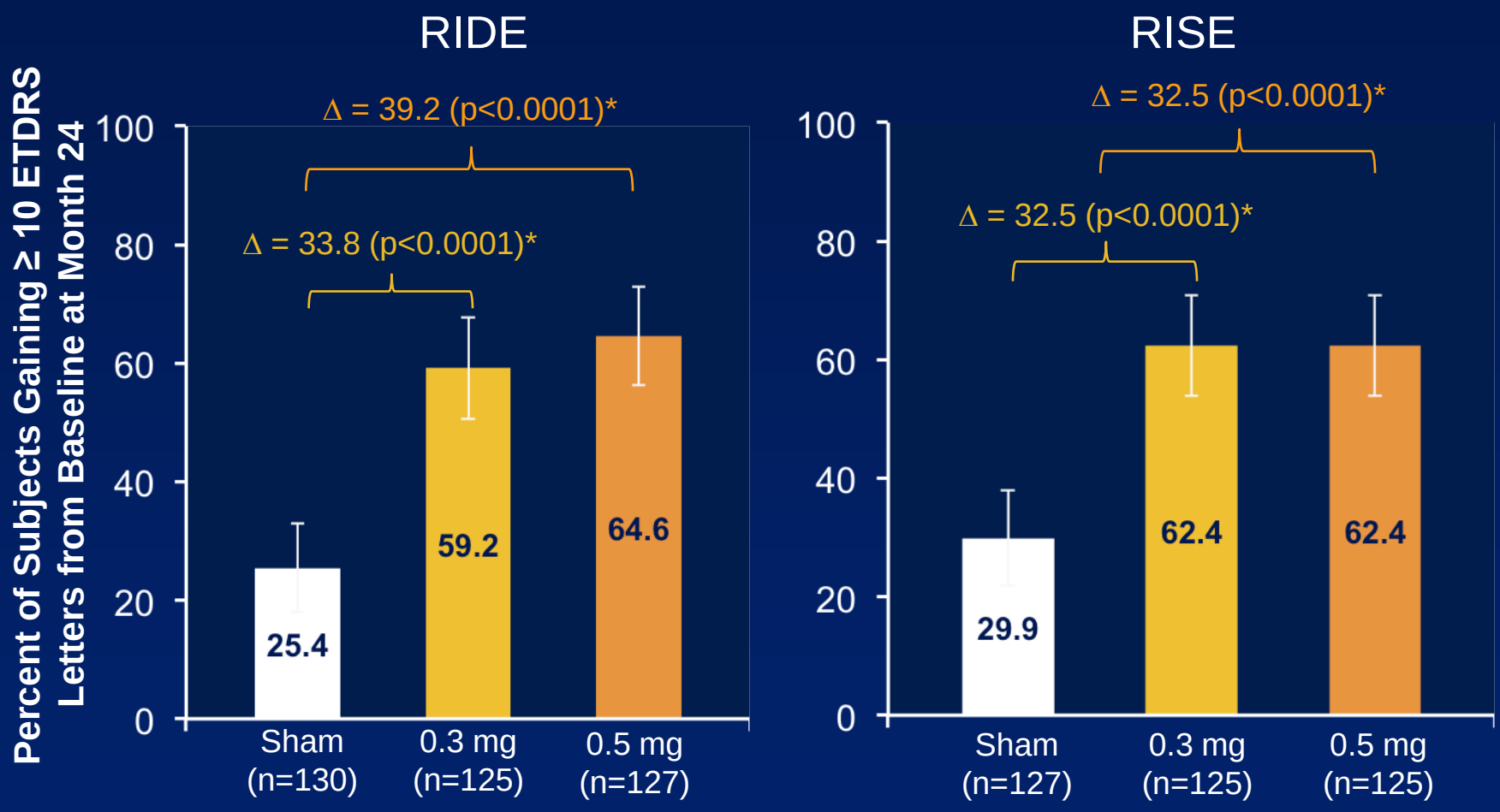
Rescue laser eligibility criteria:

- CFT ≥250 µm on OCT with <50 µm change from the prior month
- No laser in the prior 3 months
- Evaluating physician deemed laser beneficial

Panretinal photocoagulation available for all patients when clinically indicated

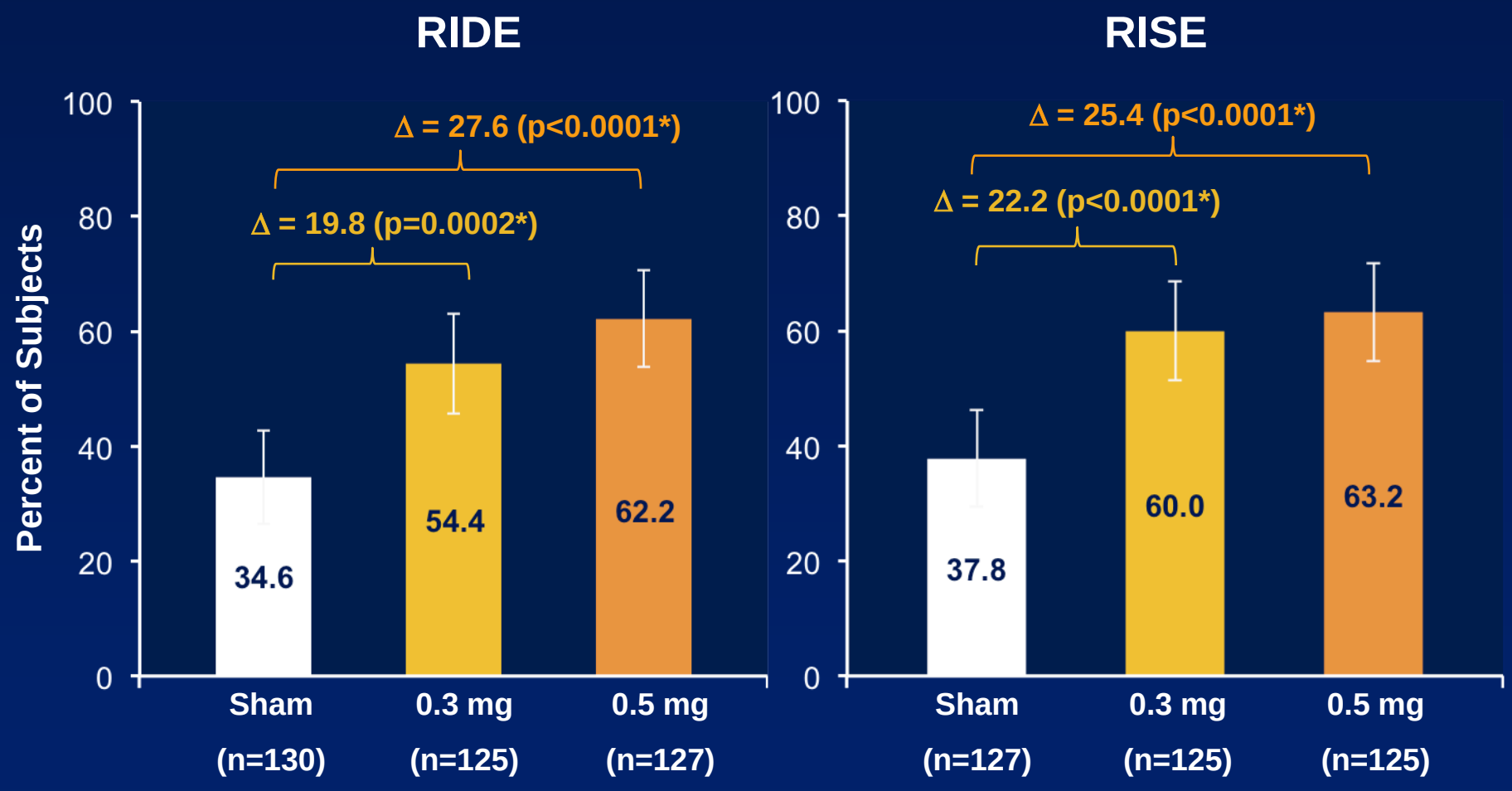
* Exploratory endpoint. Adjusted differences vs. sham were: -32.8% for the 0.3 mg group and -49.8% for the 0.5 mg group in RIDE; -35.0% for the 0.3 mg group and -39.3% for the 0.5 mg group in RISE; $p < 0.0001$ for all ranibizumab groups vs. sham (Cochran-Mantel-Haenzel chi-squared test [stratified]). SD = standard deviation. CFT = Central foveal thickness. OCT=optical coherence tomography.

Ranibizumab Treatment Leads to Clinically Meaningful Improvements in Visual Acuity in DME



Exploratory endpoint. The last observation carried forward (LOCF) imputation method was used. Vertical bars are 95% confidence interval. Reported percentages and differences vs sham are unadjusted, test and p-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA1c (≤8%, >8%) and prior treatment for DME (yes, no). ETDRS = Early Treatment Diabetic Retinopathy Study.
*Cochran-Mantel-Haenszel chi-squared test (stratified).

Significantly More Ranibizumab-Treated Patients Achieved Driving-Level Vision (20/40 or Better) at Month 24



The last observation carried forward (LOCF) imputation method was used. Vertical bars are 95% confidence interval. Reported percentages and differences vs sham are unadjusted, test and p-value are adjusted for Baseline visual acuity (≤55, >55 letters), baseline HbA1c (≤8%, >8%) and prior treatment for DME (yes, no).
*Cochran-Mantel-Haenszel chi-squared test (stratified).
ETDRS = Early Treatment Diabetic Retinopathy Study.

Contrast Sensitivity Is an Important Measure of Visual Function Addressing Quality of Vision

- Assessed using specialized eye chart[1]

Normal

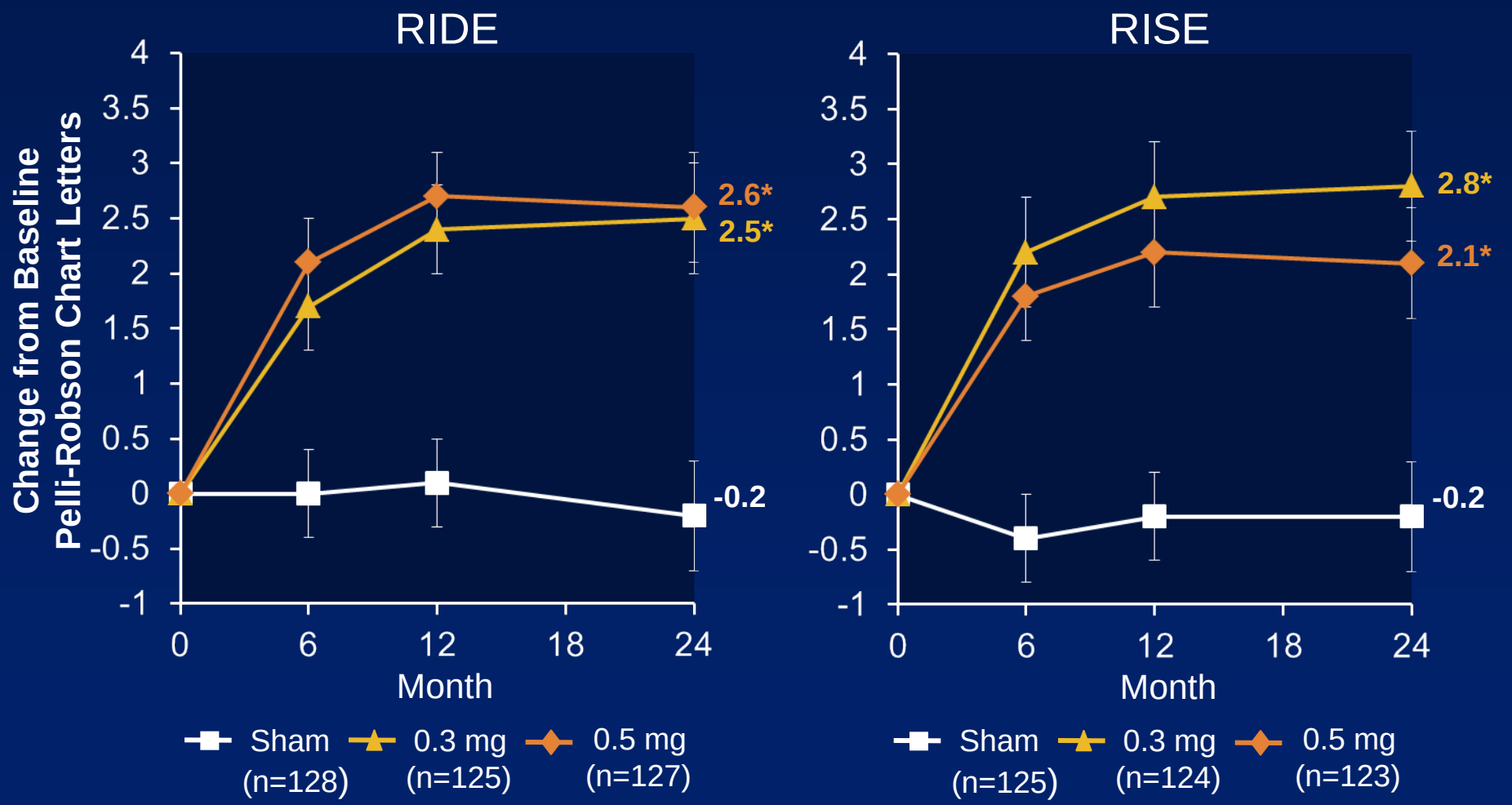
Reduced contrast

Pelli-Robson Chart

1. Pelli DG et al. *Clin Vis Sci* 1988;2:187-199

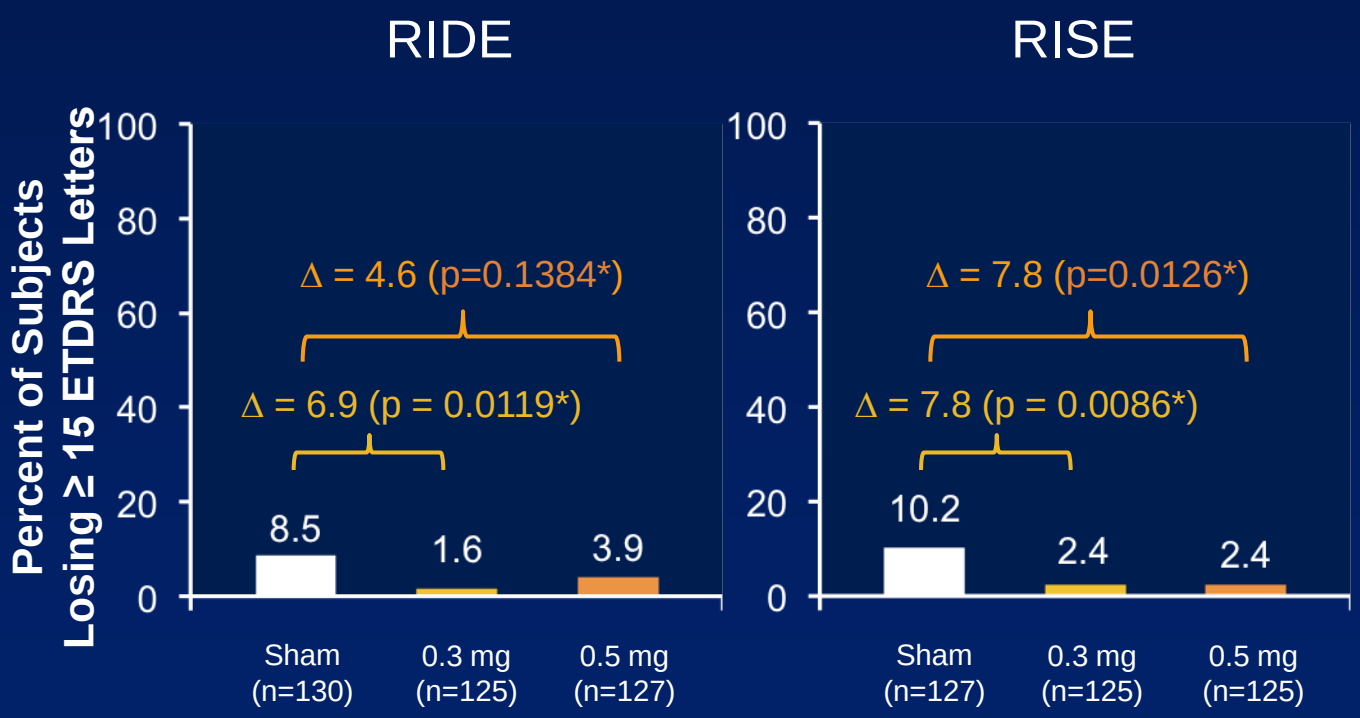
Ranibizumab Treatment Significantly Improves Contrast Sensitivity in DME

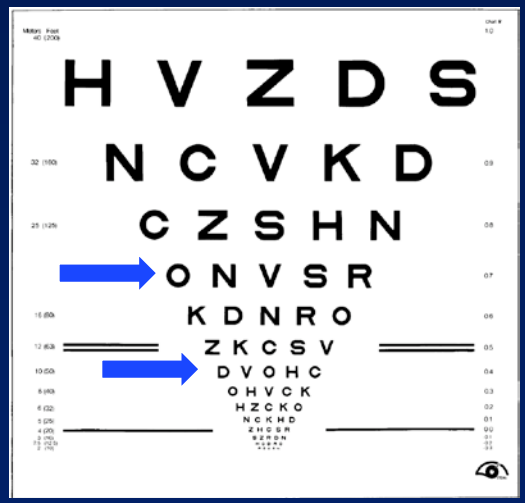
Contrast Sensitivity Change Over Time



Exploratory endpoint. *p≤0.0001 vs. sham (ANCOVA t-test [stratified]). Stratification variables in stratified analyses: baseline visual acuity (<=55, >55 letters); baseline HbA1c (<=8%, >8%); and prior therapy for DME (yes, no). The ANCOVA model includes the baseline contrast sensitivity as a covariate and the stratification variables. Vertical bars are ±1 standard error of the mean.

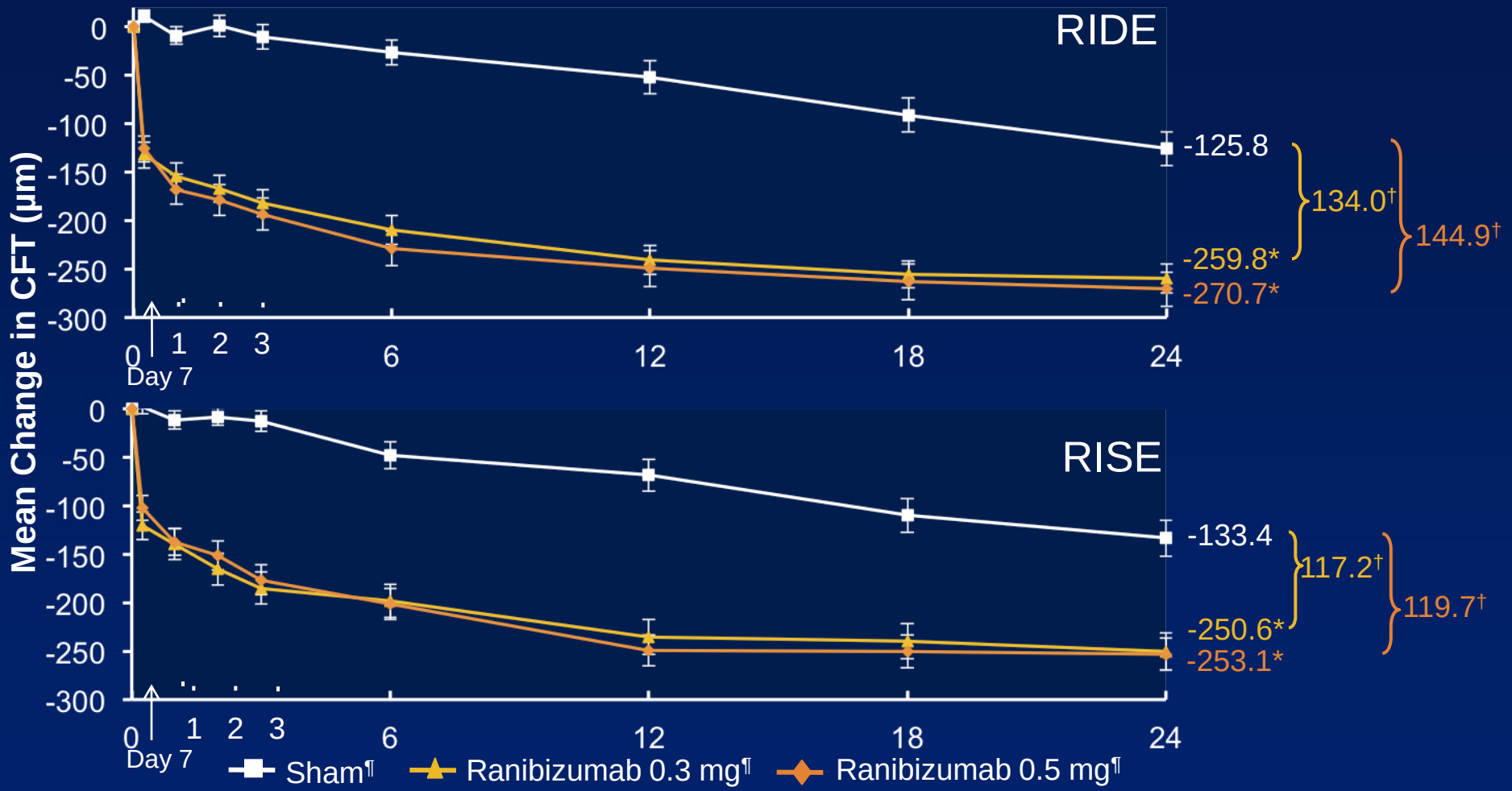
Fewer Ranibizumab-Treated Patients Experienced Significant Vision Loss after 24 Months in DME





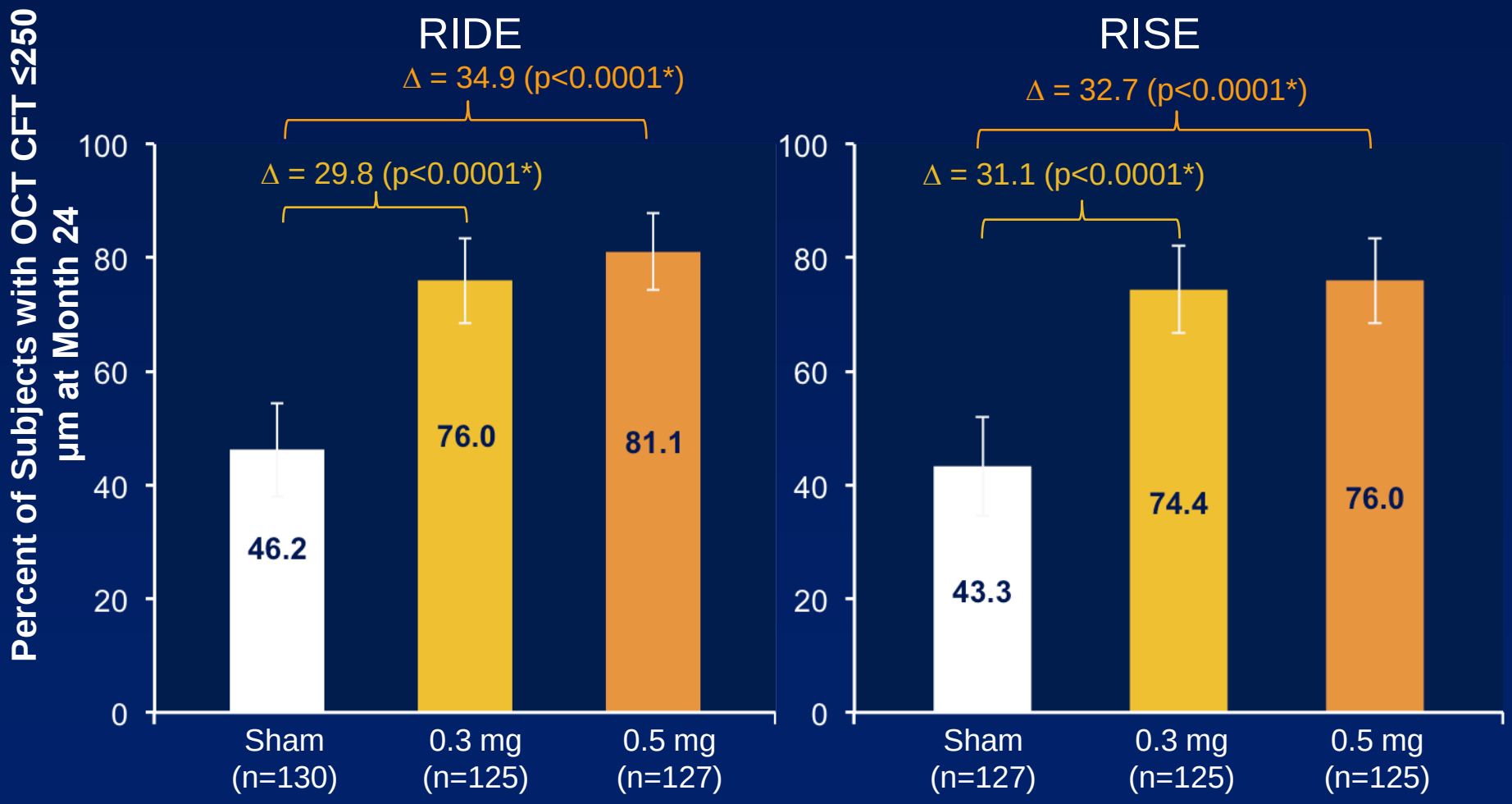
The last observation carried forward (LOCF) imputation method was used. Vertical bars are 95% confidence interval. Reported percentages and differences vs sham are unadjusted, test and p-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA1c (≤8%, >8%) and prior treatment for DME (yes, no). ETDRS = Early Treatment Diabetic Retinopathy Study.
*Cochran-Mantel-Haenszel chi-squared test (stratified).

Ranibizumab Significantly Improves Retinal Anatomy by Reducing Macular Edema on OCT in DME



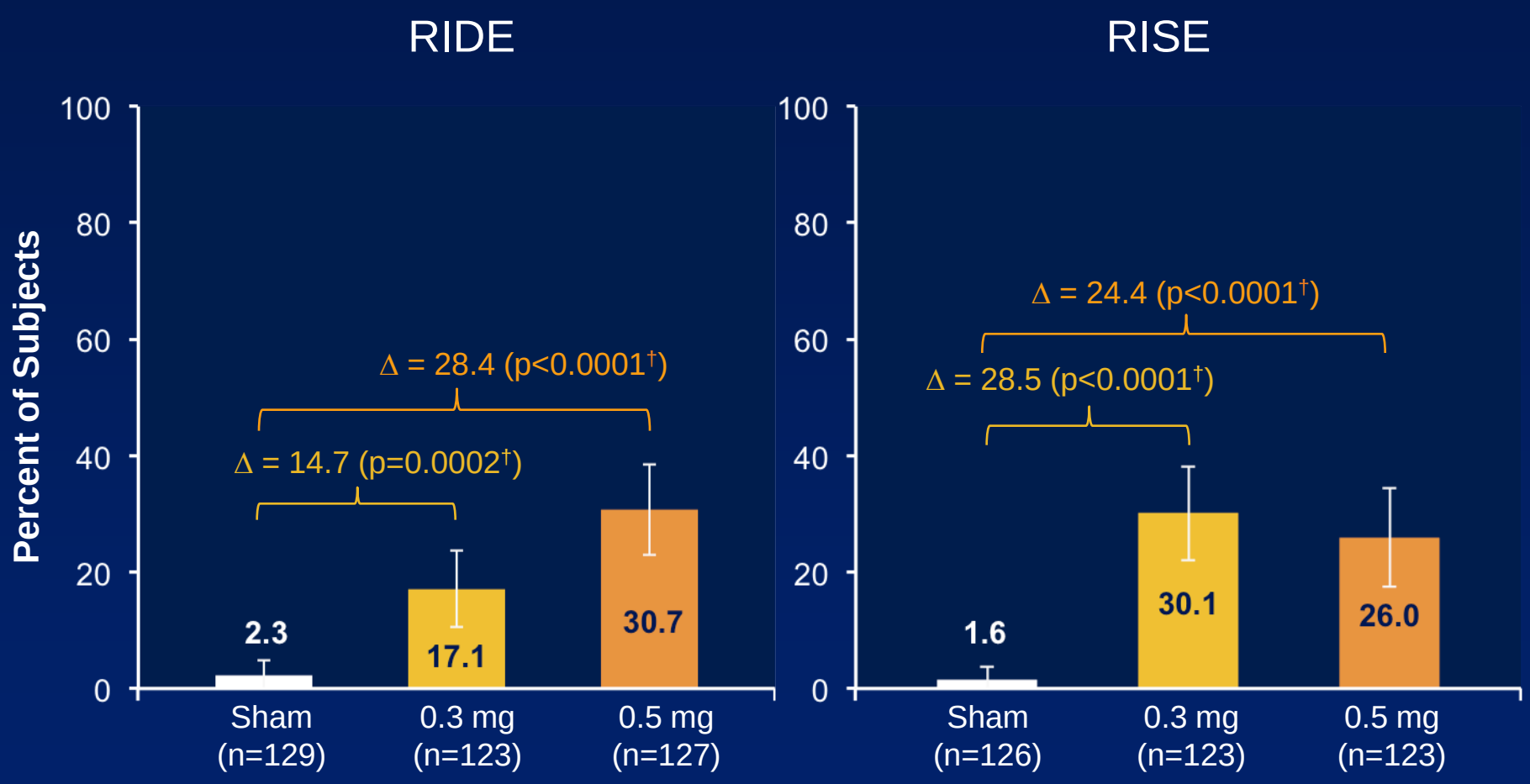
*p<0.0001 vs. sham (ANCOVA t-test [stratified]). Earliest statistically significant difference at Day 7. The ANCOVA model includes the baseline CFT as a covariate and the stratification variables baseline VA (≤ 55, > 55 ETDRS letters), baseline HbA1c (≤ 8%, > 8%) and prior treatment for DME (yes, no). †Unadjusted differences in means. Vertical bars are ±1 standard error of the mean. Central foveal thickness (CFT) is defined as center point thickness. Independent review of optical coherence tomography performed at University of Wisconsin Fundus Photograph Reading Center. ¶ Sham/0.3mg/0.5mg: RIDE (n=130/125/127), RISE (n=127/125/125).

Ranibizumab Treatment Is Significantly More Likely to Result in Resolution of Macular Edema on Optical Coherence Tomography



The last observation carried forward (LOCF) imputation method was used. Vertical bars are 95% confidence interval. Reported percentages and differences vs sham are unadjusted, test and p-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA1c (≤8%, >8%) and prior treatment for DME (yes, no). ETDRS = Early Treatment Diabetic Retinopathy Study.
*Cochran-Mantel-Haenszel chi-squared test (stratified).

Ranibizumab Treatment is Significantly More Likely to Result in Resolution of Macular Edema on Fluorescein Angiography



* Defined as total area of fluorescein leakage of 0 disc areas on reading-center evaluated angiograms. The last observation carried forward (LOCF) imputation method was used. Vertical bars are 95% confidence interval. Reported percentages and differences vs sham are unadjusted, test and p-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA1c (≤8%, >8%) and prior treatment for DME (yes, no).
ETDRS = Early Treatment Diabetic Retinopathy Study.
† Cochran-Mantel-Haenszel chi-squared test (stratified).

Fewer Serious Ocular Events Related to Diabetic Retinopathy with Ranibizumab Compared to Sham

- Ocular safety consistent with Phase III studies of ranibizumab in non-DME patients

SAEs, n (%) MedDRA High Level Term or Preferred Term	RIDE & RISE (Pooled)		
		Ranibizumab	
	Sham (n=250)	0.3 mg (n=250)	0.5 mg (n=250)
Any Serious Adverse Event	16 (6.4)	8 (3.2)	19 (7.6)
Cataract	0	1 (0.4)	2 (0.8)
Cataract Traumatic	0	1 (0.4)	2 (0.8)
Endophthalmitis	0	2 (0.8)	2 (0.8)
Intraocular Pressure Increased	0	0	1 (0.4)
Retinal Detachment	1 (0.4)	0	1 (0.4)
Retinal Tear	0	0	1 (0.4)
Uveitis	0	1 (0.4)	0
Vitreous Haemorrhage	7 (2.8)	0	2 (0.8)
Visual Acuity Reduced	4 (1.6)	0	3 (1.2)

* MedDRA = Medical Dictionary for Regulatory Activities, Version 13.1, SAE = Serious Adverse Event

Low Rates of Serious Adverse Events Potentially Related to Systemic VEGF Inhibition

- Generally similar across groups, and numerically highest in sham group, although stroke was slightly higher in 0.5 mg ranibizumab group

Category / Event , n (%)	Sham (n=250)	Ranibizumab 0.3 mg (n=250)	Ranibizumab 0.5 mg (n=250)
Any event	25 (10.0)	19 (7.6)	22 (8.8)
Arterial Thromboembolic Events	20 (8.0)	13 (5.2)	16 (6.4)
Myocardial Infarction*	9 (3.6)	9 (3.6)	7 (2.8)
Angina Pectoris	1 (0.4)	0	1 (0.4)
Angina Unstable	2 (0.8)	0	0
CVA+	4 (1.6)	3 (1.2)	8 (3.2)†
Transient Ischaemic Attack	5 (2.0)	1 (0.4)	1 (0.4)
Hypertension	1 (0.4)	3 (1.2)	6 (2.4)
Non−Ocular Haemorrhage	5 (2.0)	2 (0.8)	2 (0.8)
Proteinuria	1 (0.4)	1 (0.4)	1 (0.4)
Ischemic colitis	0	2 (0.8)	1 (0.4)
Large Intestine Perforation	0	0	1 (0.4)

* Myocardial infarction includes preferred terms of acute myocardial infarction and myocardial infraction.
† Includes one subject assigned to sham who had a stroke (2008), received a single dose of 0.5mg RBZ in error (2009), and died of unknown cause (2010).
+ CVA = cerebrovascular accident, includes preferred terms of cerebrovascular accident, ischaemic stroke, and lacunar infarction.

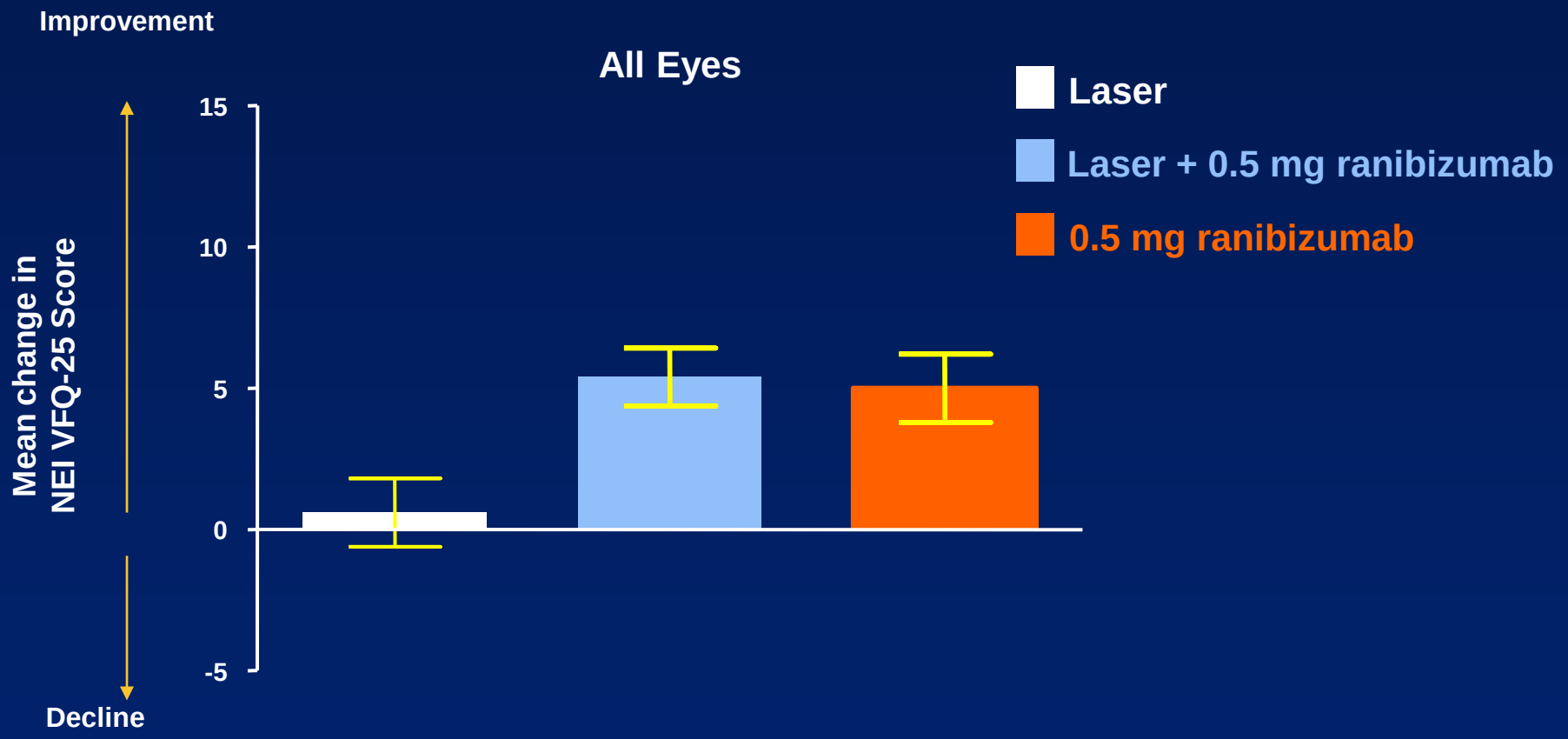
APTC Events (Vascular Deaths, Deaths of Unknown Cause, Non-fatal MI, Non-Fatal CVA)

- APTC events similar among sham and 0.3 mg ranibizumab, slightly higher in 0.5 mg
- Deaths from any cause slightly higher in ranibizumab groups
- Increases in stroke and/or death not seen in other large, Phase III studies of 0.5 mg ranibizumab in patients with DME (DRCR.net and Novartis RESTORE studies)

Category / Event , n (%)	Sham (n=250)	Ranibizumab	
		0.3 mg (n=250)	0.5 mg (n=250)
Total APTC events*	13 (5.2)	14 (5.6)	18 (7.2)
Deaths, overall	3 (1.2)	7 (2.8)	11 (4.4)
Vascular death	3 (1.2)	5 (2.0)	6 (2.4)
Unknown cause	0	0	1 (0.4)†
Nonfatal MI	7 (2.8)	7 (2.8)	6 (2.4)
Nonfatal CVA	3 (1.2)	2 (0.8)	5 (2.0)

*Includes vascular deaths, deaths of unknown cause, nonfatal MIs, and nonfatal CVAs.
†Includes one RISE subject assigned to sham who had a stroke (2008), received a single dose of 0.5mg RBZ in error (2009), and died of unknown cause (2010). Subject assigned to 0.5mg RBZ group for safety analyses per pre-specified analysis population criteria.
APTC = Antiplatelet Trialists' Collaboration; CVA = cerebrovascular accident; MI = myocardial infarction.

In RESTORE, Greater Improvements Observed in Patient-reported Visual Function Outcomes in Ranibizumab-treated Patients (NEI VFQ-25)



*RESTORE NEI VFQ-25 Composite Score: Mean Change From Baseline at 12 Months. Data based on full analysis set: N=110, 118, 115.
Vertical bars are ± one standard error of the mean.
RESTORE: Mitchell P et al. *Ophthalmology* 2011;118:615–625.

Ranibizumab Has Been Well Studied in DME

Published Phase II and Phase III Clinical Trials for Ranibizumab in DME *(current as of February 14, 2012)*

RIDE/RISE (Phase III Genentech-Sponsored Studies)

1. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for Diabetic Macular Edema: Results from 2 Phase III Randomized Trials. Ophthalmology, E-pub Date: [published online ahead of print] 2012. DOI #10.1016/j.ophtha.2011.12.039.
2. Ip MS, et al. Long-term Effects of Ranibizumab on Diabetic Retinopathy Severity and Progression. Submitted.

DRCR.net Protocol I (Phase III DRCR.net-Sponsored Study)

3. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064-1077.
4. Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118:609-614.
5. Diabetic Retinopathy Clinical Research Network. Rationale for the Diabetic Retinopathy Clinical Resarch Network Intravitreal Anti-VEGF Treatment and Follow-up Protocol for Center-Involved Diabetic Macular Edema. Ophthalmology 2011;118;e5-e14.

RESTORE (Phase III Novartis-Sponsored Study)

6. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615-625.

RESOLVE (Phase II Novartis-Sponsored Study)

7. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study*): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 2010;33:2399-2405.

READ-2 (Phase II Investigator-Sponsored Study)

8. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the macula in diabetes (READ-2) study. Ophthalmology 2010;117:2146-2151.
9. Nguyen QD, Shah SM, Heier JS, et al. Primary end point (six months) results of the Ranibizumab for Edema of the Macula in Diabetes (READ-2) study. Ophthalmology 2009;116:2175-2181.e1.

DRCR.net Protocol J (Phase III Short-term DRCR.net-Sponsored Study)

10. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. Retina 2011;31:1009-1027.