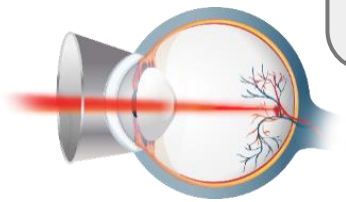
Aflibercept Main Studies in Diabetic Macular Edema(DME)

למידע נוסף והתוויות יש לפנות לעלון לרופא המעודכן כפי שפורסם ע"י משרד הבריאות

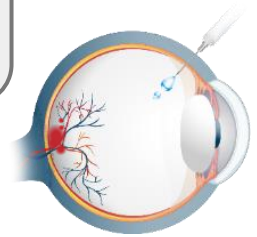
The VIVID and VISTA studies assessed the efficacy of Aflibercept in patients with DME

VIVID & VISTA



VIVID (N=406) and VISTA (N=466)[1]

Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320



Patients randomized 1:1:1

Laser photocoagulation[a] (focal or grid)

Aflibercept 2q4 (dosing every month)

Aflibercept 2q8[b] (dosing every other month)

Primary endpoint:
Mean change in BCVA from baseline at Week 52

Week 52 (Year 1):
Primary endpoint

Continued treatment through Week 148 (Year 3)

Secondary endpoints included:
Proportion of eyes that:
Gained ≥15 letters
Had ≥2-step improvement in DRSS

a. After Week 100, patients treated with laser were eligible to receive aflibercept treatment.[2] b.After 5 initial monthly doses.

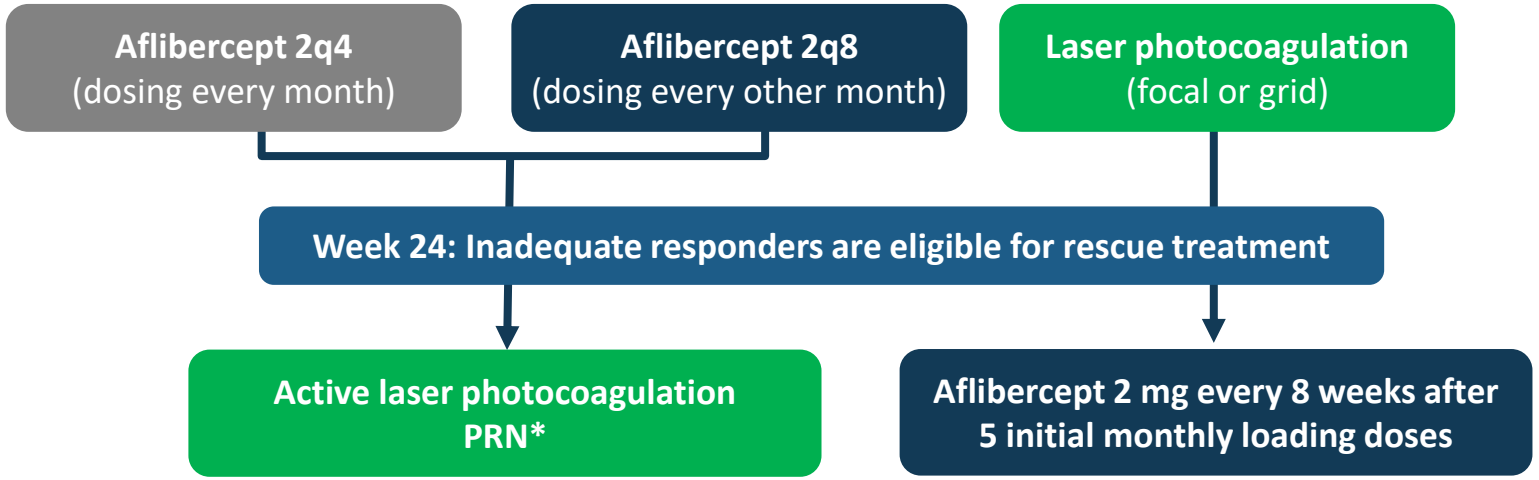
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; DME, diabetic macular edema; DRSS, diabetic retinopathy severity score; ETDRS, Early Treatment Diabetic Retinopathy Study.

1. Korobelnik J-F *et al. Ophthalmology* 2014; 121 (11): 2247–2254. 2. Heier JS *et al. Ophthalmology* 2016; 123 (11): 2376–2385.

Additional treatment for inadequate responders

VIVID & VISTA

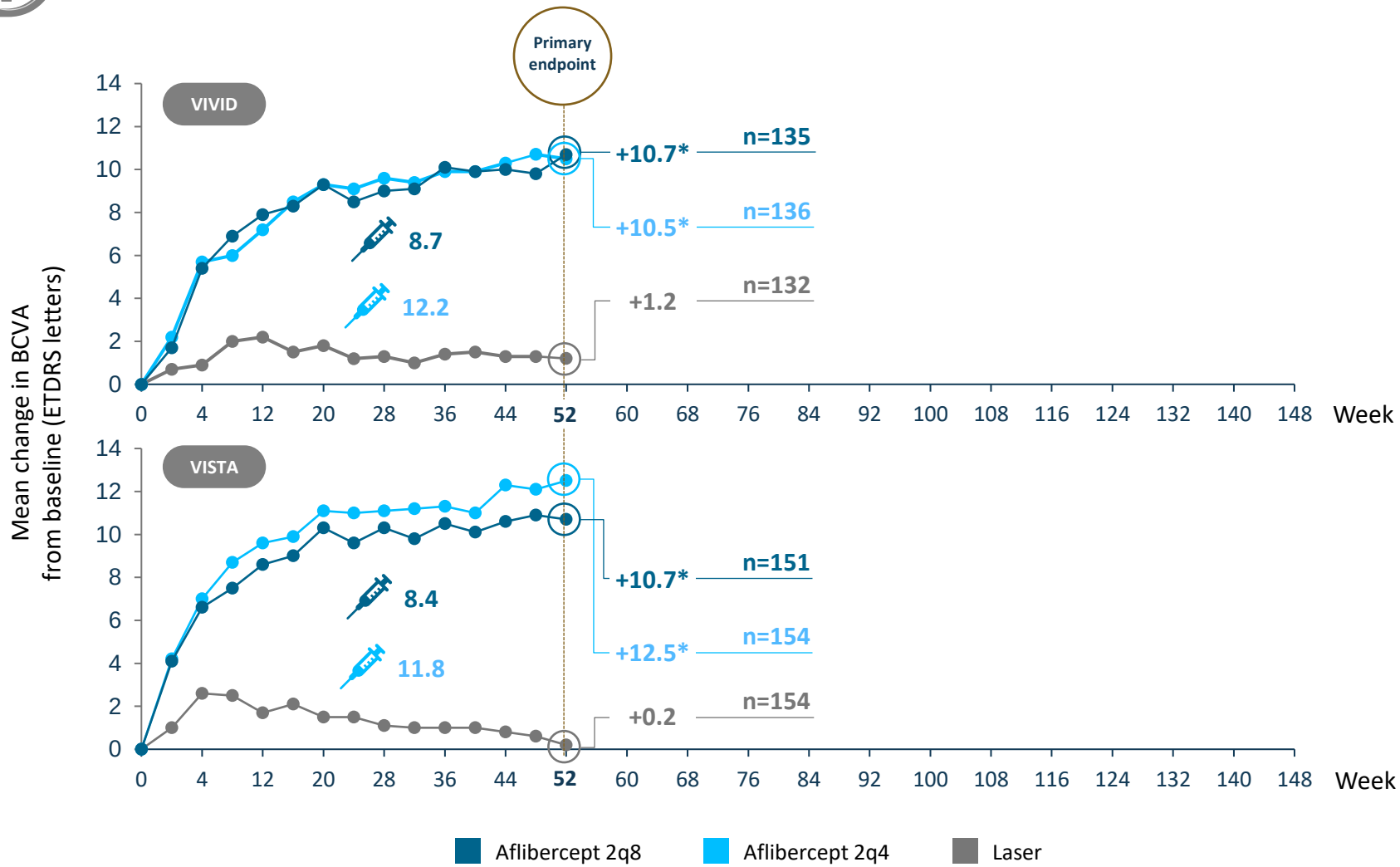
- All study participants were considered for additional active (rescue) treatment from Week 24
- Inadequate response was defined as:
  - A loss of ≥10 letters on two consecutive visits or ≥15 letters at any one visit from the best previous measurement, and BCVA worse than baseline



*Patients in the laser group were eligible to receive aflibercept 2 mg PRN during Year 3.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; BCVA, best corrected visual acuity; PRN, *pro re nata* (as needed).
Korobelnik J-F *et al. Ophthalmology* 2014; 121 (11): 2247–2254.

Results : Aflibercept was superior to laser photocoagulation in terms of vison gains

VIVID & VISTA



BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. *P<0.0001 vs. laser

1. Korobelnik J-F, et al. *Ophthalmology*. 2014;121(11):2247-2254. **2**. Brown DM, et al. *Ophthalmology*. 2015;122(10):2044-2052. **3**. Heier JS, et al. *Ophthalmology*. 2016;123(11):2376-2385.

Results : vision gains achieved with aflibercept treatment in year 1 were maintained over 148 weeks, with fewer injections in years 2 & 3

VIVID & VISTA

BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. *P<0.0001 vs. laser

1. Korobelnik J-F, et al. *Ophthalmology*. 2014;121(11):2247-2254. **2**. Brown DM, et al. *Ophthalmology*. 2015;122(10):2044-2052. **3**. Heier JS, et al. *Ophthalmology*. 2016;123(11):2376-2385.

VIVID and VISTA: Ocular Serious Adverse Events from baseline to Week 148

N (safety analysis set)	Laser[a] 287	Aflibercept 2q4 291	Aflibercept 2q8[b] 287	Aflibercept overall 578
Any ocular SAEs in study eye, n,%	18 (6.3%)	25 (8.6%)	18 (6.3%)	43 (7.4%)
Vitreous haemorrhage	5 (1.7%)	4 (1.4%)	3 (1.0%)	7 (1.2%)
Cataract	1 (0.3%)	9 (3.1%)	6 (2.1%)	15 (2.6%)
Retinal detachment	0	3 (1.0%)	2 (0.7%)	5 (0.9%)
Retinal vascular disorder	1 (0.3%)	2 (0.7%)	0	2 (0.3%)
Visual acuity reduced	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Diabetic retinal oedema	0	1 (0.3%)	0	1 (0.2%)
Hyphaema	0	1 (0.3%)	0	1 (0.2%)
Lens dislocation	0	1 (0.3%)	0	1 (0.2%)
Punctate keratitis	0	1 (0.3%)	0	1 (0.2%)
Retinal artery occlusion	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Retinal ischaemia	0	1 (0.3%)	0	1 (0.2%)
Cataract subcapsular	1 (0.3%)	0	2(0.7%)	2 (0.3%)
Corneal epithelium defect	1 (0.3%)	0	0	0
Diabetic retinopathy	4 (1.4%)	0	0	0
Retinal haemorrhage	1 (0.3%)	0	0	0
Endophthalmitis	0	2 (0.7%)	1 (0.3%)	3 (0.5%)
Intraocular pressure increased	0	0	1 (0.3%)	1 (0.2%)
Visual field defect	0	0	1 (0.3%)	1 (0.2%)

2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; DME, diabetic macular edema; DRSS, diabetic retinopathy severity score; ETDRS, Early Treatment Diabetic Retinopathy Study.
Heier JS *et al*. *Ophthalmology* 2016; 123 (11): 2376–2385. a. After Week 100, patients treated with laser were eligible to receive aflibercept treatment.[2] b.After 5 initial monthly doses.

VIVID and VISTA: APTC Events from baseline to Week 148

	Laser	Aflibercept 2q4	Aflibercept 2q8	Aflibercept overall
N	287	291	287	578
Any APTC event, n (%)	22 (7.7%)	31 (10.7%)	21 (7.3%)	52 (9.0%)
Non-fatal MI	9 (3.1%)	10 (3.4%)	9 (3.1%)	19 (3.3%)
Non-fatal stroke	10 (3.5%)	11 (3.8%)	7 (2.4%)	18 (3.1%)
Vascular deaths	4 (1.4%)	11 (3.8%)	6 (2.1%)	17 (2.9%)

2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; DME, diabetic macular edema; DRSS, diabetic retinopathy severity score; ETDRS, Early Treatment Diabetic Retinopathy Study; APTC=Anti-platelet trialists' Collaboration

Heier JS *et al*. *Ophthalmology* 2016; 123 (11): 2376–2385.

VIVID and VISTA studies: Summary through Week 148

- In VIVID and VISTA, patients treated with aflibercept achieved substantial vision gains from baseline, compared with laser:
  - At the Week 52 primary endpoint, patients treated with aflibercept had gained more than 10 letters from baseline[1]
  - At Week 20, after 5 monthly doses of aflibercept, patients gained more than 9 letters from baseline and this gain was maintained with q8 dosing until Week 148[2]
- Visual and anatomic improvements with aflibercept were maintained through 148 weeks[3]
- Over 80% of patients in the laser arm required rescue treatment with aflibercept from Week 24 to Week 100[3]
- Patients in the laser arm achieved modest vision gains after Week 100 when PRN aflibercept treatment became available[3]
- Safety outcomes were in line with the established safety profile of aflibercept

DRSS, diabetic retinopathy severity score; PRN, *pro re nata* (as needed); q8, every 8 weeks.

1. Korobelnik J-F *et al. Ophthalmology* 2014; 121 (11): 2247–2254. 2. Bayer data on file. 3. Heier JS *et al. Ophthalmology* 2016; 123 (11): 2376–2385. 4. Brown DM *et al. Ophthalmology* 2015; 122 (10): 2044–2052.

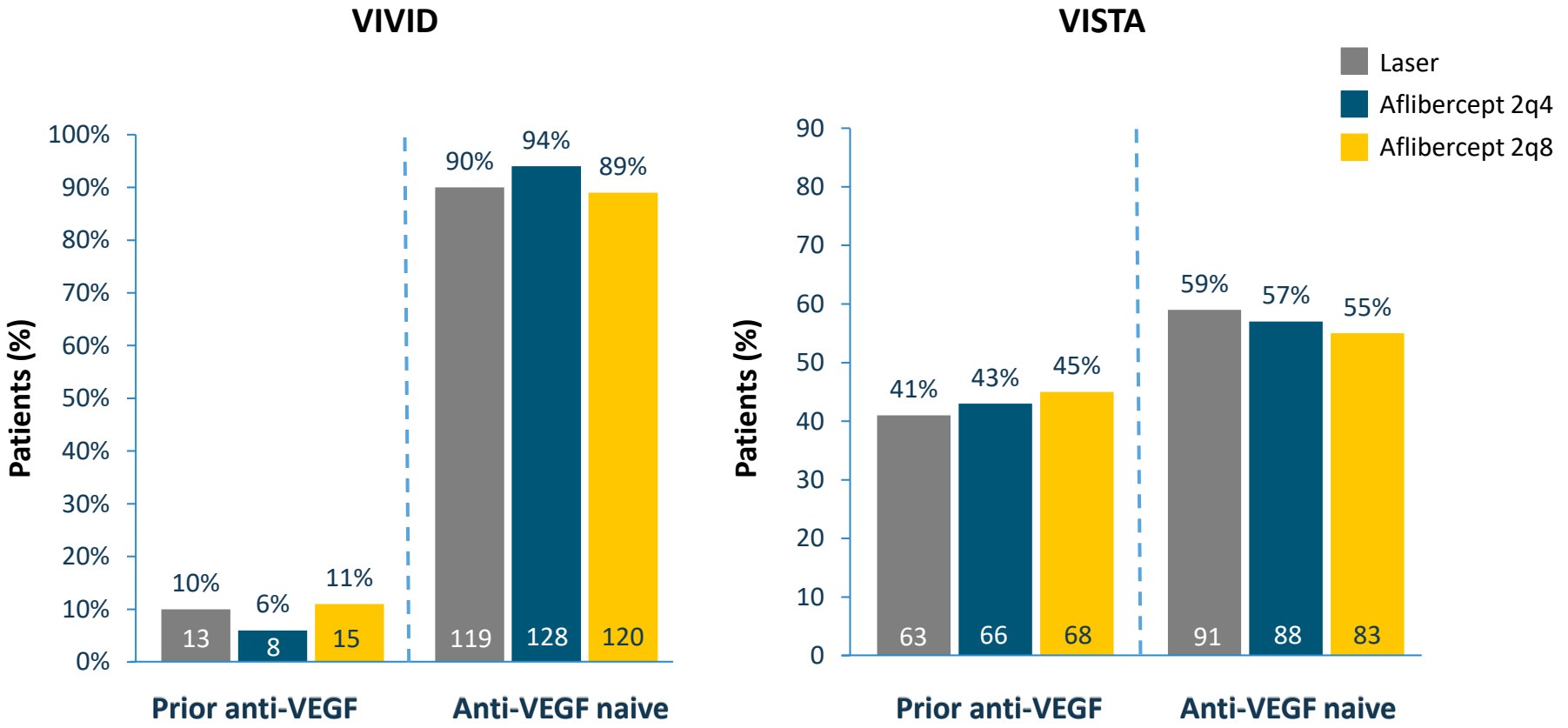
VIVID and VISTA studies :Subgroup analyses

Intravitreal Aflibercept Injection in Diabetic Macular Edema Patients with and without Prior Anti-Vascular Endothelial Growth Factor Treatment: Outcomes from the Phase 3 Program

Do DV *et al*. *Ophthalmology* 2016; 123 (4): 850–857

Proportion of patients with prior anti-VEGF treatment

VISTA Subgroup analyses



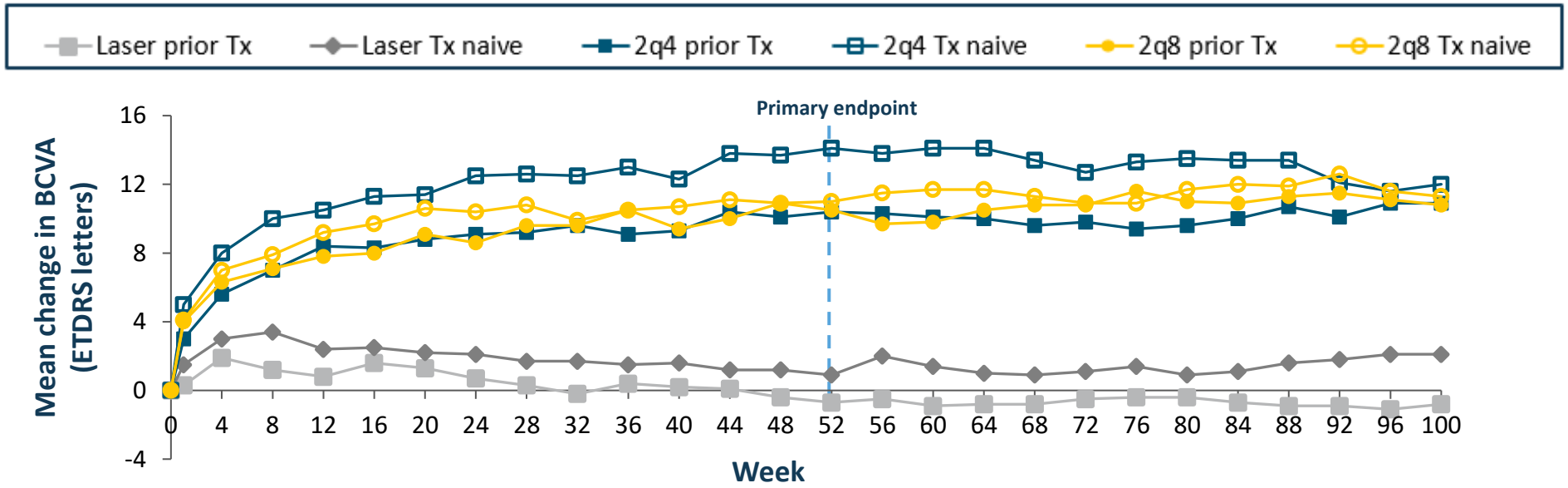
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; VEGF, vascular endothelial growth factor.

Korobelnik J-F *et al. Ophthalmology* 2014; 121 (11): 2247–2254.

Mean change in BCVA from baseline in patients with and without prior anti-VEGF treatment

VISTA Subgroup analyses

VISTA study



	Laser		2q4		2q8	
	Prior treatment	Treatment naive	Prior treatment	Treatment naive	Prior treatment	Treatment naive
n	63	91	67	87	68	83
Mean change in BCVA (52 weeks)	**–0.7**	**0.9**	**10.4**	**14.1**	**10.5**	**11.0**
Mean change in BCVA (100 weeks)	**–0.8**	**2.1**	**10.9**	**12.0**	**10.8**	**11.3**

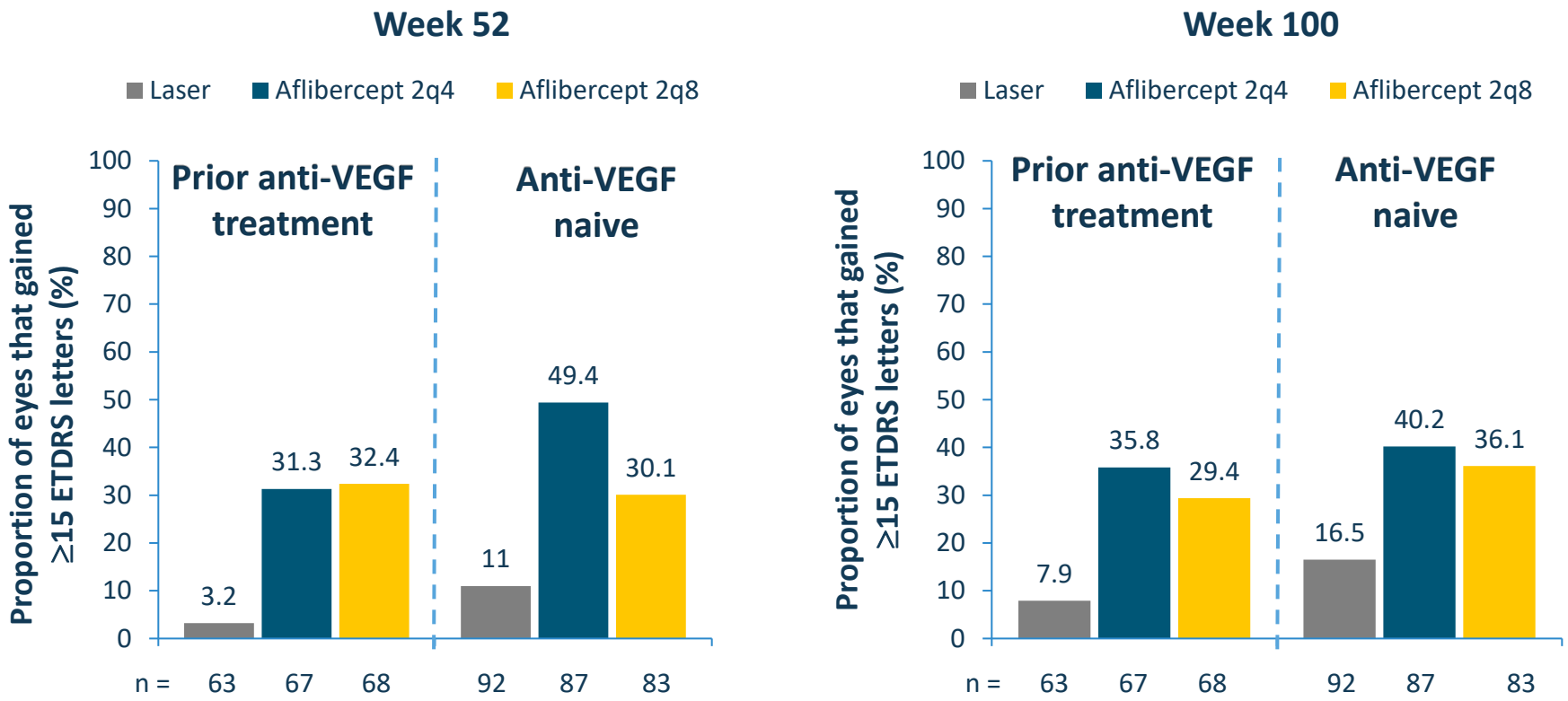
Full analysis set; LOCF.

2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; Tx, treatment; VEGF, vascular endothelial growth factor. Do DV *et al*. *Ophthalmology* 2016; 123 (4): 850–857.

VISTA Subgroup analyses

Proportion of eyes gaining ≥15 ETDRS letters from baseline

VISTA study

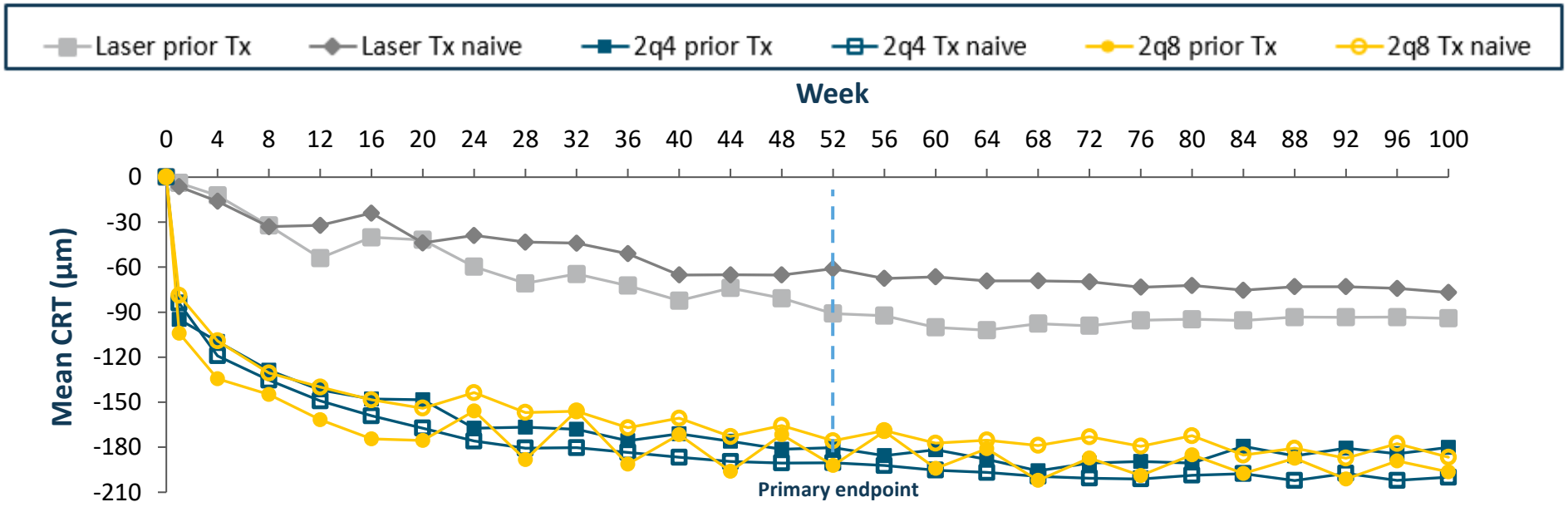


Full analysis set; LOCF.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; VEGF, vascular endothelial growth factor.
Do DV *et al*. *Ophthalmology* 2016; 123 (4): 850–857.

Mean change in CRT from baseline in patients with and without prior anti-VEGF treatment

VISTA Subgroup analyses

VISTA study



	Laser		2q4		2q8	
	Prior treatment	Treatment naive	Prior treatment	Treatment naive	Prior treatment	Treatment naive
n	63	91	67	87	68	83
Mean change in CRT (Week 52)	**–90.9**	**–61.0**	**–180.2**	**–190.3**	**–192.2**	**–175.5**
Mean change in CRT (Week 100)	**–94.1**	**–76.9**	**–180.1**	**–200.0**	**–196.4**	**–186.7**

Full analysis set; LOCF.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; CRT, central retinal thickness; LOCF, last observation carried forward; Tx, treatment; VEGF, vascular endothelial growth factor.
Do DV *et al*. *Ophthalmology* 2016; 123 (4): 850–857.

VISTA study Subgroup analyses: Summary

- This post hoc analysis from the VISTA study demonstrates that aflibercept is an effective treatment for DME, regardless of prior anti-VEGF therapy
- Irrespective of whether patients had received prior anti-VEGF treatment, visual and anatomic outcomes through Week 100 were similar between the 2q8 and 2q4 groups
- No new safety signals were identified

2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

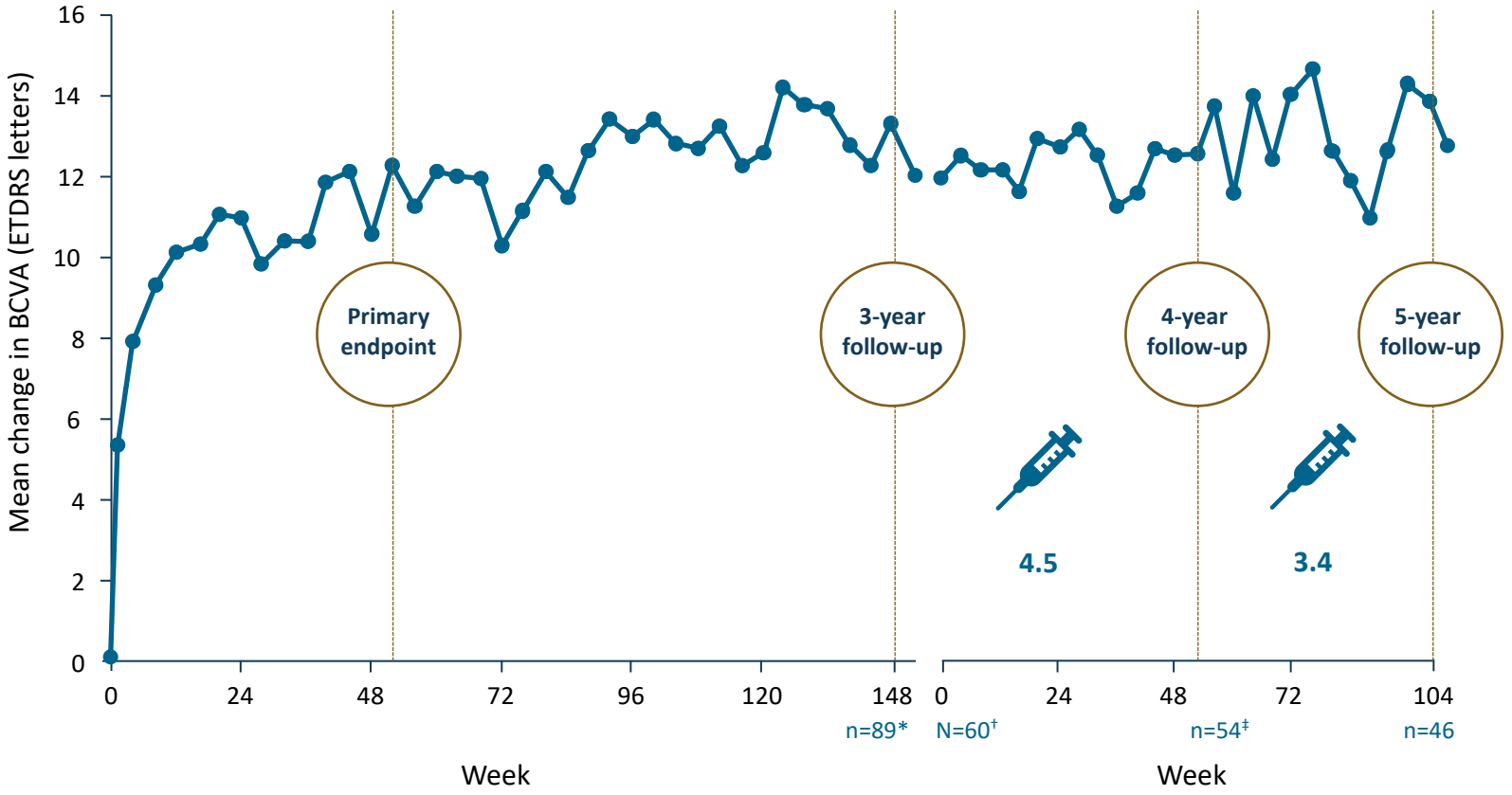
Do DV *et al*. *Ophthalmology* 2016; 123 (4): 850–857.

In ENDURANCE, with mandatory and continued follow-up, patients from VISTA receiving aflibercept maintained VA gains up to 5 years

ENDURANCE

VISTA: Mean change in BCVA from baseline through year 3[1]

ENDURANCE: Mean change in BCVA from year 3 through year 5[1]



Aflibercept

Through 2 years (of ENDURANCE), 25% of patients required no retreatment and 48% of patients received 5 or fewer injections.

*Patients completing the VISTA trial. †Patients who completed the VISTA trial were eligible to enrol in ENDURANCE. ‡At Week 52 in the ENDURANCE extension study.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity

1. Wykoff CC, et al. *Br J Ophthalmol*. 2018;102(5):631-636.

Protocol T was a randomized head-to-head trial of anti-VEGF treatment for visual impairment due to DME

PROTOCOL T

Protocol T (N=660)
Interventional, randomized, multicenter study in patients with type 1 or type 2 diabetes, DME with central involvement, and BCVA 78–24 letters (approximate Snellen equivalent: 20/32 to 20/320)

One eye from each patient randomized 1:1:1

2 mg intravitreal aflibercept (every 4 weeks*)

1.25 mg intravitreal bevacizumab (every 4 weeks*)

0.3 mg intravitreal ranibizumab (every 4 weeks*)

Primary outcome: Week 52

Change in VA from baseline to Year 1, adjusted for baseline VA using intent-to-treat principle

(Year 2: Visits occur every 4–16 weeks depending on disease status and treatment)

Bevacizumab is not licensed for intravitreal use. The licensed dose for ranibizumab in Europe is 0.5 mg

*Treatment decision based on OCT and VA criteria; pre- and post-injection topical antibiotics were given at the discretion of the investigator.

BCVA, best corrected visual acuity; DME, diabetic macular edema; OCT, optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. Wells JA *et al. Ophthalmology* 2016; 123 (6): 1351–1359.

Protocol T followed a PRN regimen with strict retreatment criteria

PROTOCOL T

- Patients were scheduled to receive sham or study drug every 4 weeks
- If improvement/worsening* was observed from the last intravitreal injection, the patient was **INJECTED**
- If no improvement/worsening* was observed after two consecutive intravitreal injections and the patient's condition was described as 'normal',† treatment was **DEFERRED**
- If no improvement/worsening was observed after two consecutive intravitreal injections and the patient's condition was described as not normal:
  - Prior to the Week 24 visit, the patient was **INJECTED**
  - At and beyond the Week 24 visit, treatment was **DEFERRED**

Patients therefore received approximately 6 monthly loading doses

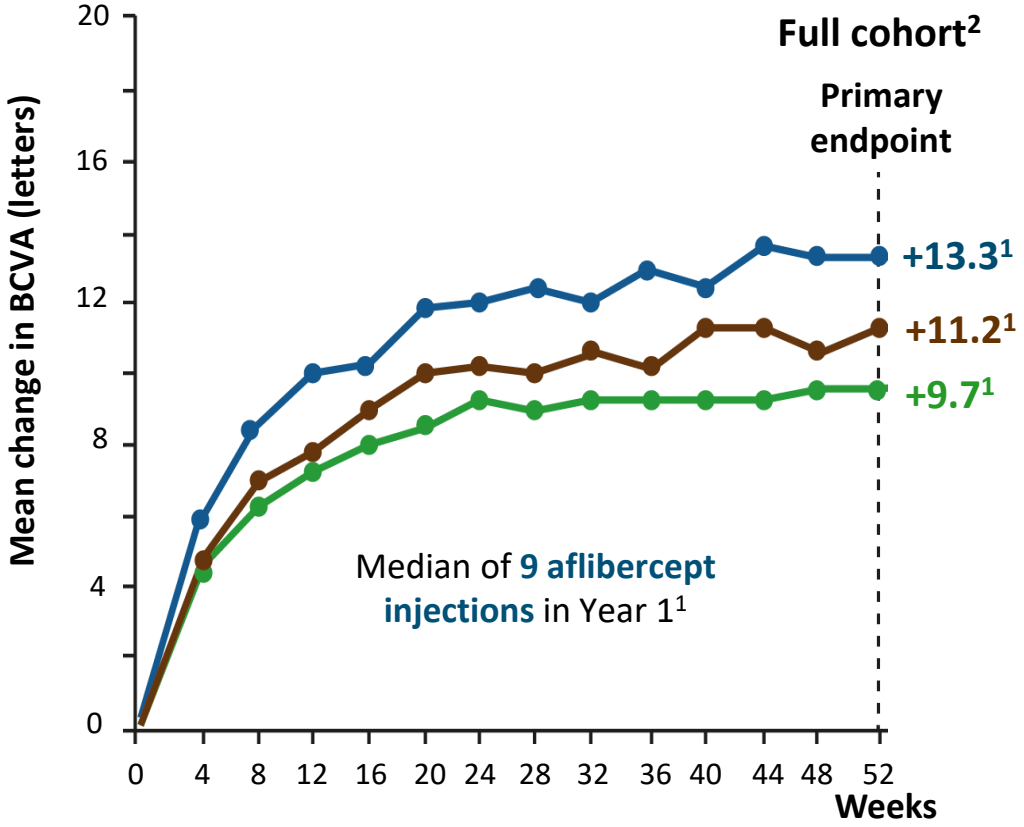
*Improvement was defined as ≥5-letter gain in VA **or** ≥10% decrease in CST; worsening was defined as ≥5-letter loss in VA **or** ≥10% increase in CST. †'Normal' was defined as 20/20 VA and Stratus equivalent (gender-specific threshold) ≤250 µm CST.

CST, central subfield thickness; PRN, *pro re nata* (as needed); VA, visual acuity.

Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. Protocol T - A comparative effectiveness study on intravitreal aflibercept, bevacizumab and ranibizumab for diabetic macular edema. Available at: http://drcrnet.jaeb.org/ViewPage.aspx?PageName=Presentations. Accessed March 2018.

Patients treated with aflibercept had statistically superior vision gains at Year 1 compared with compared to ranibizumab or bevacizumab

PROTOCOL T



Week 52 treatment group comparison:*

- **Aflibercept** vs. **bevacizumab** *P*<0.001[1]
- **Aflibercept** vs. **ranibizumab** *P*=0.034[1]
- **Ranibizumab** vs. **bevacizumab** *P*=0.12[1]

Aflibercept 2 mg, n=205

Bevacizumab 1.25 mg†, n=203

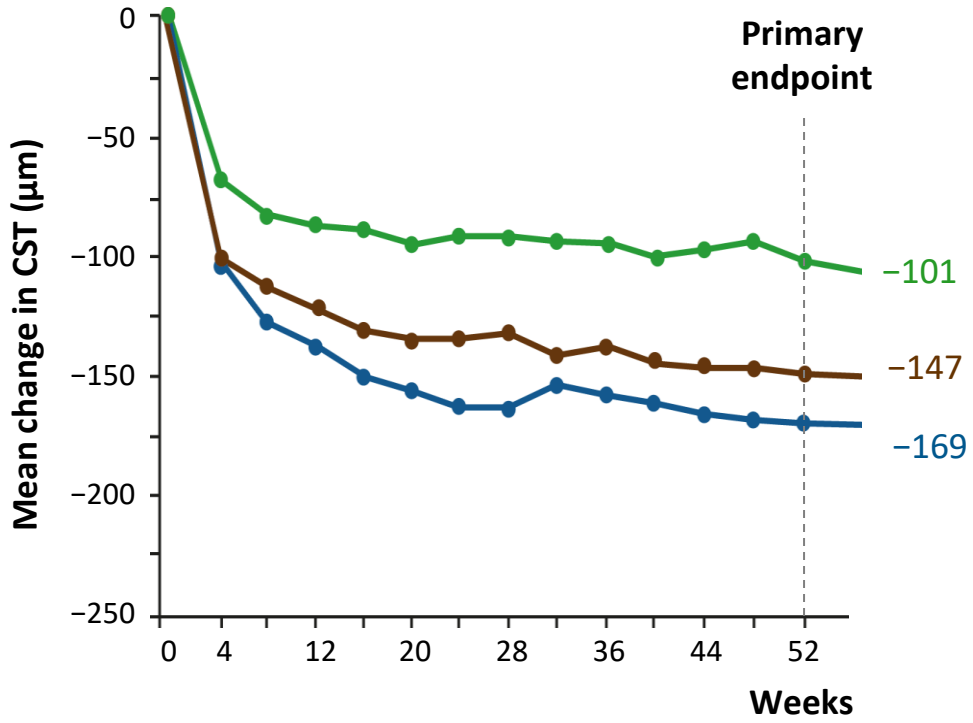
Ranibizumab 0.3 mg‡, n=201

BCVA, best corrected visual acuity; VA, visual acuity . **P*-values adjusted for baseline VA and multiple comparisons

1. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203 – supplementary appendix. 2. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

Aflibercept was associated with significant reduction in CST compared to ranibizumab and bevacizumab

PROTOCOL T



Week 52 treatment group comparison:*

- **Aflibercept** vs. **bevacizumab** *P*<0.001[2]
- **Aflibercept** vs. **ranibizumab** *P*=0.036[2]
- **Ranibizumab** vs. **bevacizumab** *P*<0.001[2]

Aflibercept 2 mg, n=205

Bevacizumab 1.25 mg†, n=203

Ranibizumab 0.3 mg‡, n=201

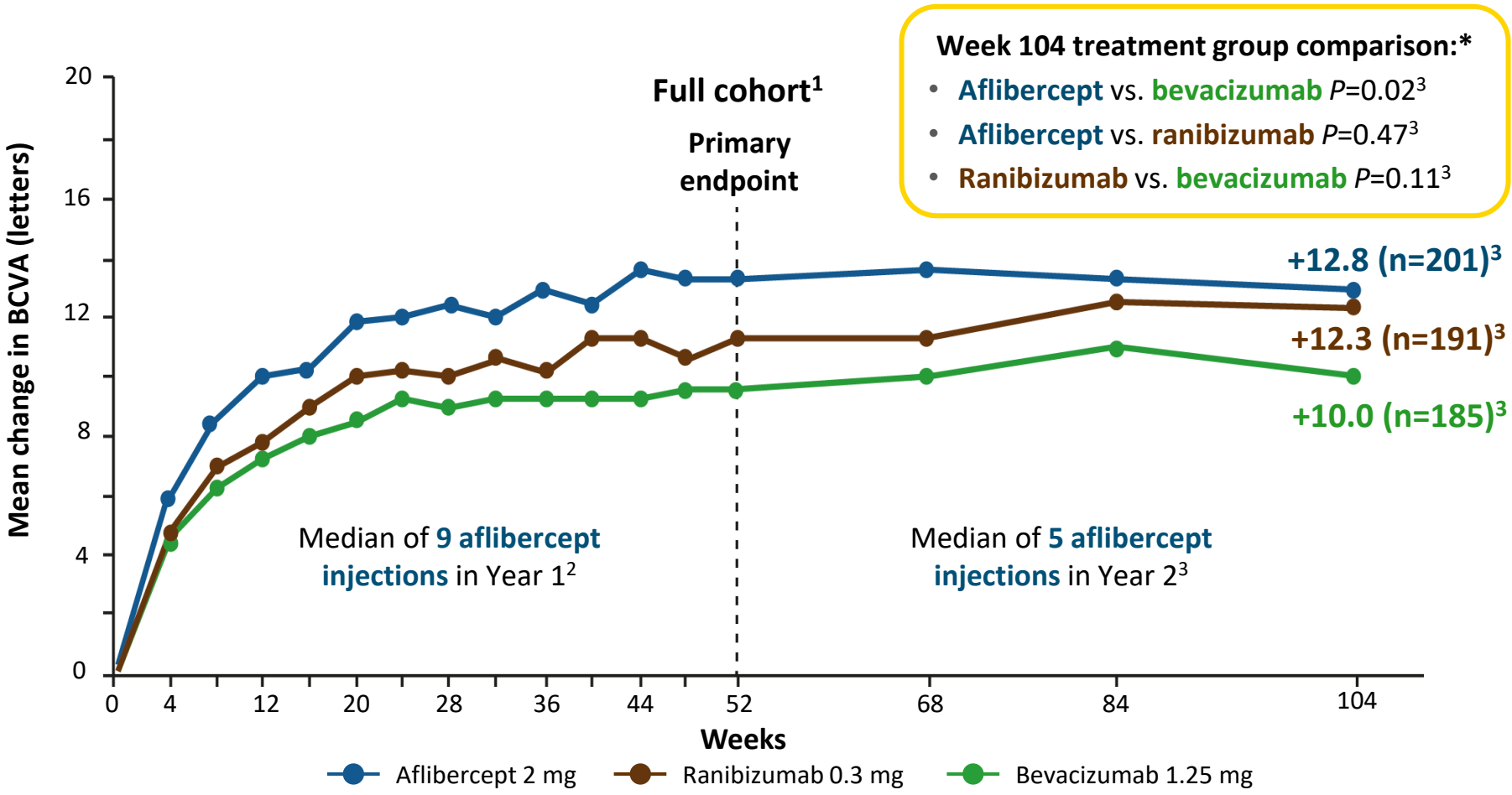
Adapted from the Diabetic Retinopathy Clinical Research Network 2015

*P-values adjusted for baseline CST and multiple comparisons. †Bevacizumab is not licensed for the treatment of visual impairment due to DME.
‡The licensed dose for ranibizumab in Europe is 0.5 mg; CST, central subfield thickness; DME, diabetic macular edema.

1. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. 2. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203 – supplementary appendix.

Initial vision gains with aflibercept were maintained to Year 2, with the need for fewer injections than in Year 1

PROTOCOL T



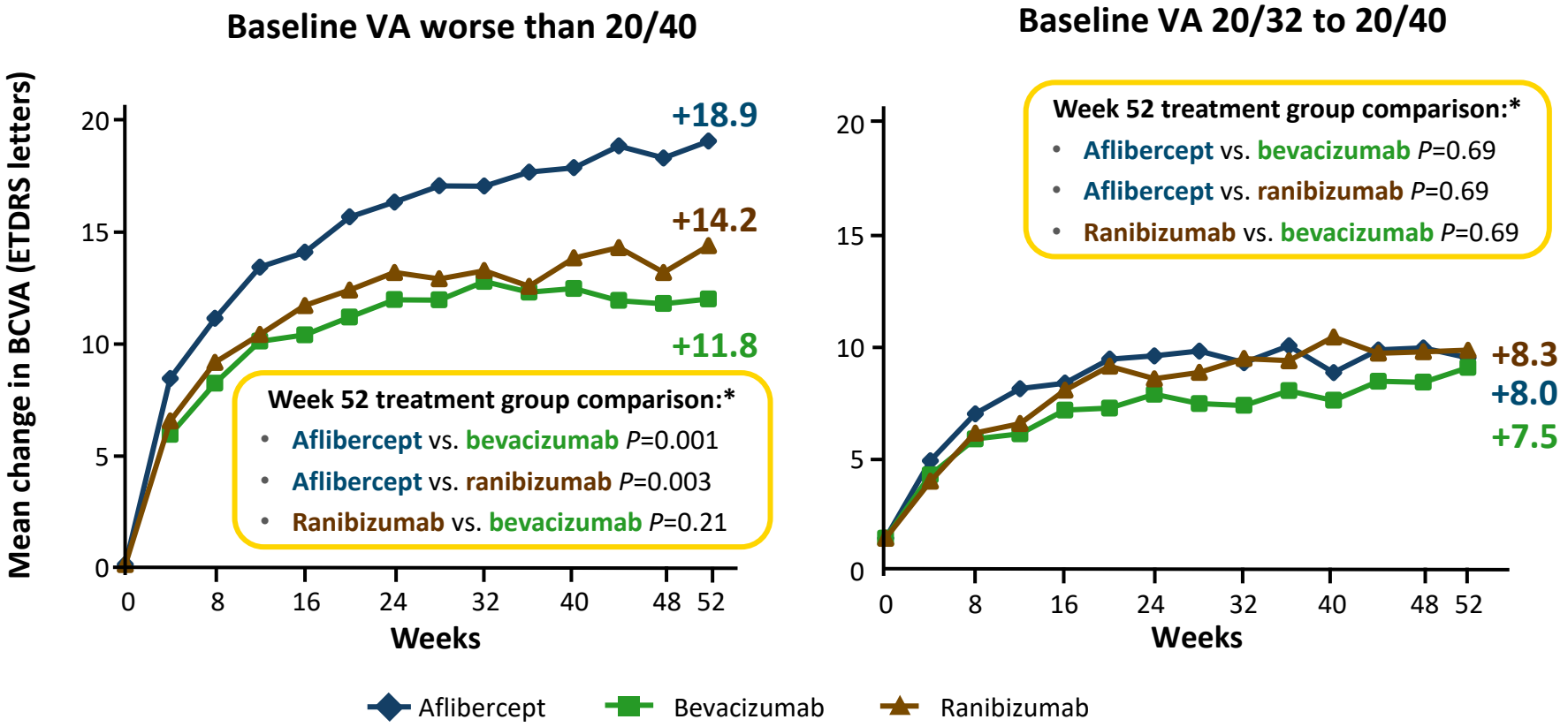
BCVA, best corrected visual acuity; VA, visual acuity. **P*-values adjusted for baseline VA and multiple comparisons.

1. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359. 2. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. 3. Wells JA *et al. Ophthalmology* 2016; 123 (6): 1351–1359 – supplementary appendix.

At Year 1, significantly greater mean vision gains were achieved with aflibercept than either comparator in patients with baseline vision worse than 20/40

PROTOCOL T

In a **prespecified analysis**, patients with baseline vision worse than 20/40 achieved significantly greater vision gains at Year 1 with aflibercept than with either comparator

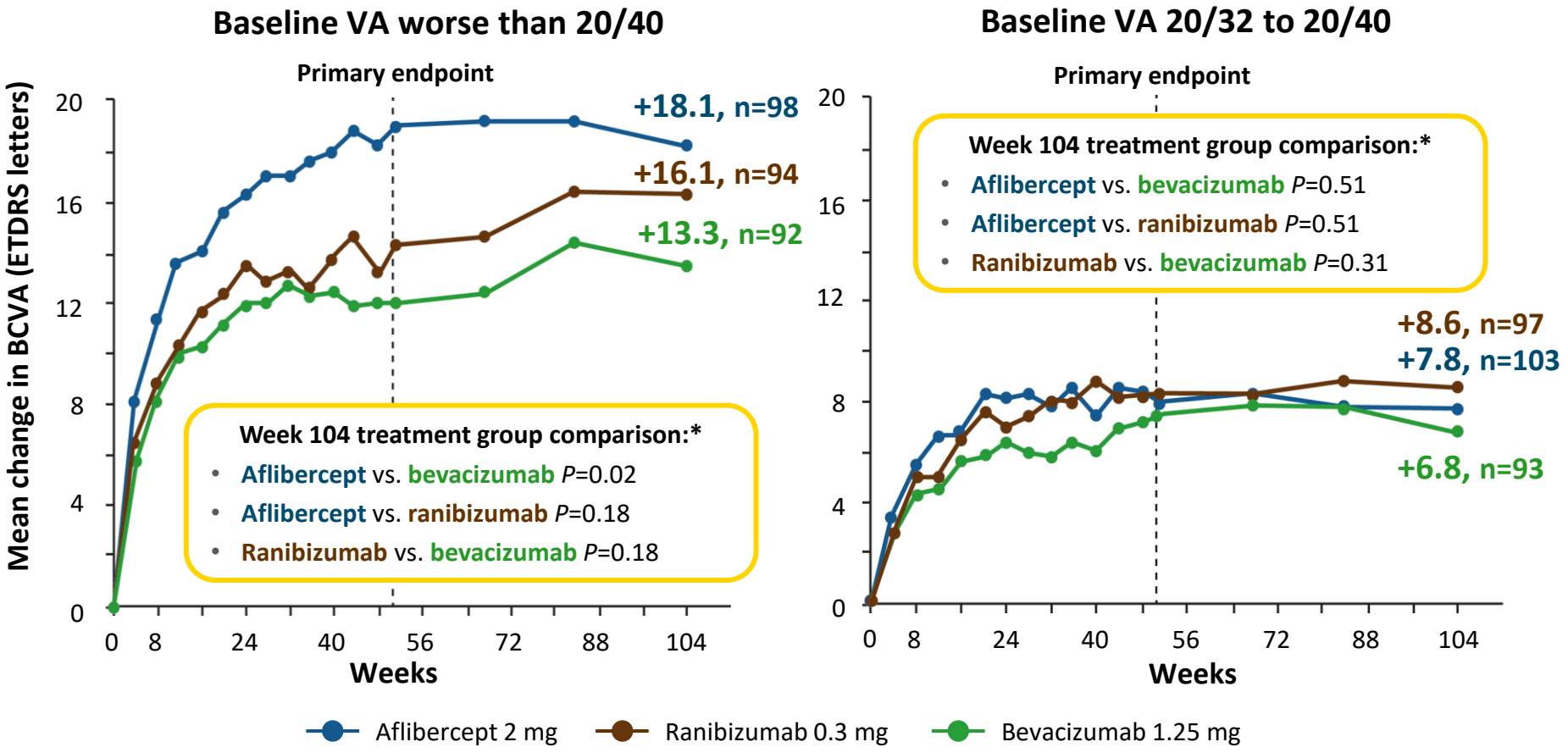


Worse than 20/40: Aflibercept n=102; bevacizumab n=102; ranibizumab n=101. **20/32 to 20/40:** Aflibercept n=106; bevacizumab n=104; ranibizumab n=105.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity. **P*-values adjusted for multiple comparisons. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203.

At Year 2, significantly greater mean vision gains were achieved with aflibercept than bevacizumab in patients with baseline vision worse than 20/40

PROTOCOL T

In a **prespecified analysis**, patients with baseline vision worse than 20/40 achieved significantly greater vision gains at Year 2 with aflibercept than with bevacizumab



BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359. . **P*-values adjusted for baseline VA and multiple comparisons

Protocol T: Focal/grid laser treatment criteria

PROTOCOL T

- Focal/grid laser can be initiated only at or after the 24-week visit if:
  - The OCT CST is ≥250 µm or there is edema threatening* the fovea (CSME)

  AND
  - The eye has not improved on OCT or VA compared with either of the last two consecutive injections

NOTE: Once focal/grid laser has been initiated, retreatment with focal/grid laser will be given unless one of the following is present:

- Focal/grid laser has been given in <13 weeks
- The OCT CST is <250 µm and there is no edema threatening the fovea
- Complete focal/grid laser has been given already
- The OCT or VA has improved since the last laser

*Edema threatening the fovea is defined as edema within 500 µm of the foveal center, or edema associated with lipid within 500 µm of the foveal center, or ≥1 disc area of edema the posterior edge of which is within 1 disc diameter of the foveal center.
CSME, clinically significant macular edema; CST, central subfield thickness; OCT, optical coherence tomography; VA, visual acuity.
Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203 – supplementary appendix.

Over the 2 years of the study, significantly fewer patients receiving aflibercept required focal/grid laser than in the comparator groups[1,2]

PROTOCOL T

	Aflibercept 2 mg	Bevacizumab† 1.25 mg	Ranibizumab 0.3 mg‡	Global *P*-value
At least one focal/grid laser				
Year 1	37%	56%	46%	<0.001*
Year 2	20%	31%	27%	0.046**
Over 2 years	41%	64%	52%	<0.001***

Patient numbers at Year 1: aflibercept = 208; bevacizumab = 206; ranibizumab = 206.
Patient numbers at Year 2: aflibercept = 201; bevacizumab = 185; ranibizumab = 191.
*Pairwise comparisons (adjusted for multiple comparisons): aflibercept–bevacizumab $P<0.001$; aflibercept–ranibizumab $P=0.06$; bevacizumab–ranibizumab $P=0.06$.
**Pairwise comparisons (adjusted for multiple comparisons): aflibercept–bevacizumab $P=0.046$; aflibercept–ranibizumab $P=0.12$; bevacizumab–ranibizumab $P=0.37$.
***Pairwise comparisons (adjusted for multiple comparisons): aflibercept–bevacizumab $P<0.001$; aflibercept–ranibizumab $P=0.04$; bevacizumab–ranibizumab $P=0.01$.
†Bevacizumab is not licensed for the treatment of visual impairment due to DME. ‡The licensed dose for ranibizumab in Europe is 0.5 mg;. 1. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203 – supplementary appendix. 2. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359 – supplementary appendix.

Treatment for DME: Anti-VEGF injection numbers (Completers of the given visit only)

PROTOCOL T

	Aflibercept 2 mg	Bevacizumab† 1.25 mg	Ranibizumab 0.3 mg‡	Global *P*-value
Median number of injections (25th, 75th percentile)				
Year 1	9 (8, 11)	10 (8, 12)	10 (8, 11)	0.045*
Year 2	5 (2,7)	6 (2, 9)	6 (2, 9)	0.32
Over 2 years	15 (11, 17)	16 (12, 20)	15 (11, 19)	0.08

NOTE: 98% of protocol-required re-injections were given over 2 years.
Patient numbers at Year 1: aflibercept = 208; bevacizumab = 206; ranibizumab = 206.
Patient numbers at Year 2: aflibercept = 201; bevacizumab = 185; ranibizumab = 192.
*Pairwise comparisons (adjusted for multiple comparisons): aflibercept–bevacizumab *P*=0.045; aflibercept–ranibizumab *P*=0.19; bevacizumab–ranibizumab *P*=0.22.
†Bevacizumab is not licensed for the treatment of visual impairment due to DME. ‡Seven study eyes received 1 injection and 2 eyes received 2 injections of 0.5 mg of ranibizumab prior to the FDA approving a 0.3 mg dose of ranibizumab for DME treatment and protocol revision to use the 0.3 mg dose. 0.3 mg ranibizumab is NOT licensed for use outside the US. DME, diabetic macular edema; FDA, Food and Drug Administration; VEGF, vascular endothelial growth factor.
Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359 – supplementary appendix.

PROTOCOL T

Systemic AEs Prespecified APTC AEs through 2 years

	Aflibercept 2 mg (n=224)	Bevacizumab† 1.25 mg (n=218)	Ranibizumab 0.3 mg‡ (n=218)
Non-fatal MI	3%	1%	3%
Non-fatal stroke	<1%	3%	5%
Death from potential vascular cause or unknown	1%	4%	4%
Any event*	5%	8%	12%

***P*=0.047**

**P*-value is for the overall three-group comparison by Fisher's exact test. Pairwise comparisons (adjusted for multiple comparisons): aflibercept–bevacizumab *P*=0.34; aflibercept–ranibizumab *P*=0.047; bevacizumab–ranibizumab *P*=0.20. Global *P*-value adjusting for gender, age at baseline, hemoglobin A1c at baseline, diabetes type, diabetes duration at baseline, insulin use, prior coronary artery disease, prior MI, prior stroke, prior transient ischemic attack, prior hypertension, and smoking status: *P*=0.09.

†Bevacizumab is not licensed for the treatment of visual impairment due to DME. ‡The licensed dose for ranibizumab in Europe is 0.5 mg

AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; DME, diabetic macular edema; MI, myocardial infarction.

Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

Post hoc analysis of APTC AEs through 2 years Stratified by prior MI/stroke

PROTOCOL T

	Aflibercept 2 mg	Bevacizumab† 1.25 mg	Ranibizumab 0.3 mg‡
No prior MI/stroke	n=203	n=193	n=193
Non-fatal MI	3%	2%	2%
Non-fatal stroke	<1%	3%	3%
Death from potential vascular cause or unknown	<1%	2%	4%
Any event	5%	6%	9%
Prior MI/stroke	n=21	n=25	n=25
Non-fatal MI	5%	0	8%
Non-fatal stroke	0	4%	20%
Death from potential vascular cause or unknown	5%	16%	8%
Any event	10%	20%	36%

Global *P*-value adjusting for prior MI and prior stroke: *P*=0.06. †Bevacizumab is not licensed for the treatment of visual impairment due to DME. ‡ The licensed dose for ranibizumab in Europe is 0.5 mg;
AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; DME, diabetic macular edema; MI, myocardial infarction. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359 – supplementary appendix.

Protocol T: Summary

PROTOCOL T

- The change in VA from baseline at 1 year (the primary endpoint) was +13.3 (aflibercept group), +11.2 (ranibizumab group), and +9.7 (bevacizumab group)[1]
  - Aflibercept vs. bevacizumab, $P<0.001$[1]
  - Aflibercept vs. ranibizumab, $P=0.034$[1]
- Vision gains improvement (from baseline) at 2 years were seen in all three groups, with approximately half the number of injections, slightly decreased frequency of visits, and decreased amounts of laser in the second year compared with Year 1[2]
- Among eyes with better VA, no differences in 2-year vision outcomes between treatment groups were identified[2]
- Among eyes with worse baseline VA:
  - Aflibercept had significantly greater 2-year VA outcomes compared with bevacizumab, although the difference was diminished at Year 2[2]
  - The difference in VA gain between aflibercept and ranibizumab that was noted at 1 year had diminished at 2 years and was no longer statistically significant[2]

VA, visual acuity.

1. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. 2. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.