Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flowchart of Study Eyes Included in Analyses

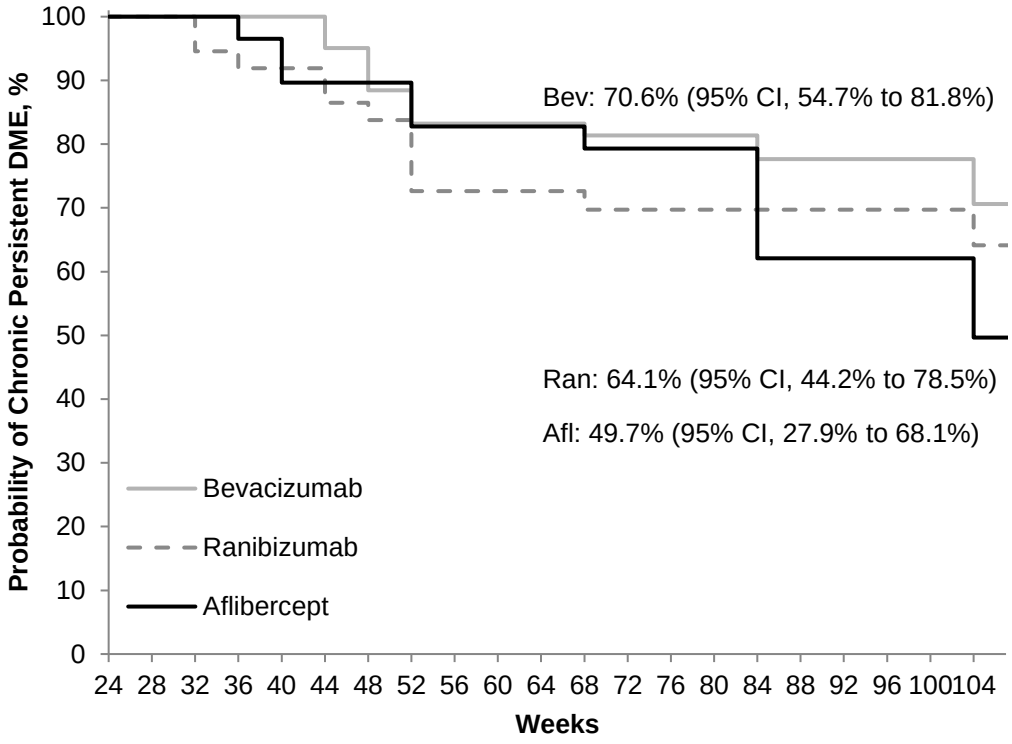
	Aflibercept	Bevacizumab	Ranibizumab
Randomized	224	218	218
↓ Baseline central-involved DME on OCT[a]	220	215	211
↓ Received at least four of the theoretical maximum of 6 injections prior to the 24-week visit (unless success after 3)	213	208	202
↓ No more than two missed visits between the 28-week and 52-week visits	198	191	187
↓ No alternative treatment prior to the 52-week visit	196	187	187
↓ Completed the 24-week visit. **Included in 24-week analyses.**	**190**	**180**	**176**
↓ Persistent DME[b] through the 24-week visit. **Included in 1-year analyses.**	**60**	**118**	**73**
↓ Completed a minimum of 4 visits in year 2	60	108	69
↓ No alternative treatment prior to the 104-week visit	59	105	69
↓ Completed the 104-week visit. **Included in 2-year analyses.**	**59**	**101**	**67**

Abbreviations: DME, diabetic macular edema; OCT, optical coherence tomography.

[a] For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 μm for women and ≥320μm for men. For Zeiss Cirrus machines, defined as central subfield thickness ≥290 μm for women and ≥305 μm for men. For Zeiss Stratus machines, defined as central subfield thickness ≥250 μm for both sexes.

[b] Central-involved DME present at each 4-week study visit, including the 24-week visit

eFigure 2. Probability of Chronic Persistent Diabetic Macular Edema Through 2 Years by Treatment Group Among Eyes With Baseline Visual Acuity Letter Score of 78 to 69 (Approximate Snellen Equivalent 20/32 to 20/40)



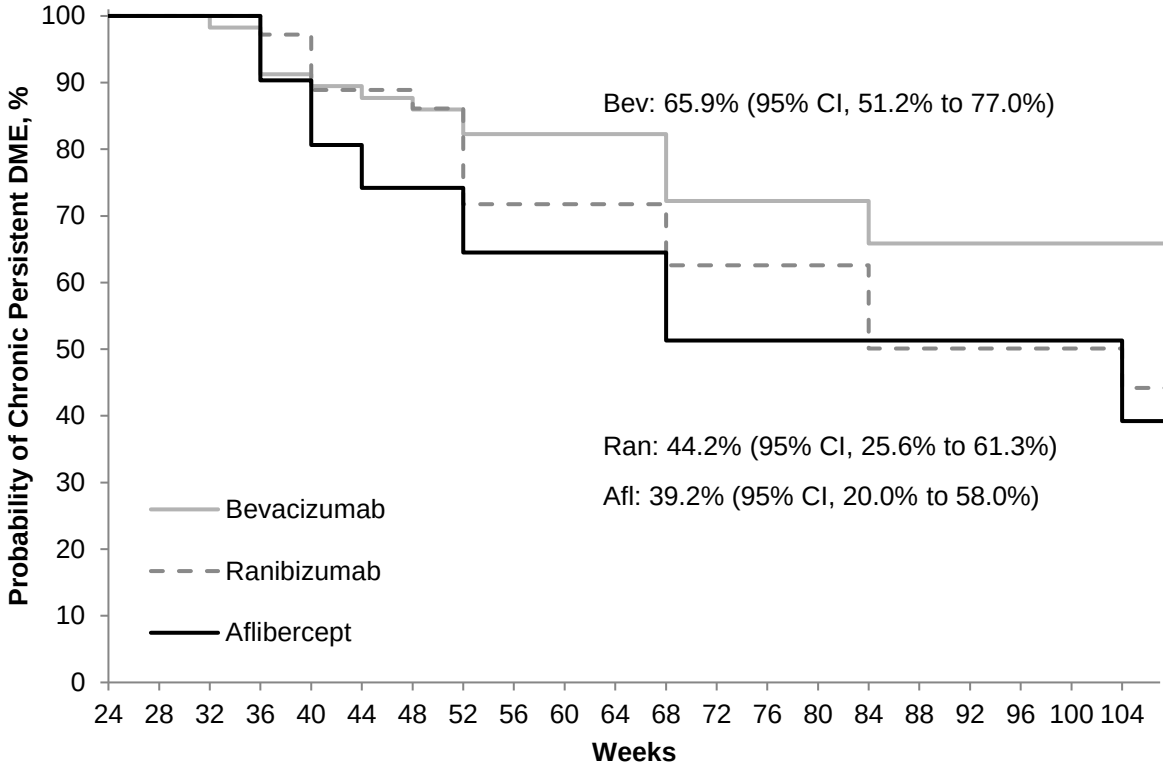
Weeks	28	32	36	40	44	48	52	68	84	104
Aflibercept										
No. of eyes at risk	29	29	29	28	26	26	26	24	23	18
No. of events	0	0	1	2	0	0	2	1	5	2
Bevacizumab										
No. of eyes at risk	61	61	61	61	61	58	53	45	44	42
No. of events	0	0	0	0	3	4	3	1	2	2
Ranibizumab										
No. of eyes at risk	37	37	35	34	34	32	31	25	24	24
No. of events	0	2	1	0	2	1	4	1	0	1

Time-To-Event Analysis for Resolution of Chronic Persistent DME Adjusted for Baseline Vision and Central Subfield Thickness

Comparison	Hazard Ratio (95% Confidence Interval)	*P*-value
Aflibercept vs. Bevacizumab	2.08 (0.83 to 5.24)	.17
Aflibercept vs. Ranibizumab	1.30 (0.59 to 2.86)	.52
Ranibizumab vs. Bevacizumab	1.61 (0.66 to 3.90)	.46

eFigure 2 Legend: Eyes in which chronic persistent DME did not resolve by 104 weeks were censored on the date of their last visit (N = 81), the date of first non-protocol DME treatment (N = 0), or on the date of the 52-week visit if there were less than 4 visits in year 2 (N = 6). Two-year life-table survival estimates are shown for each group. Solid black = aflibercept, solid gray = bevacizumab, dashed gray = ranibizumab. An event was defined as central subfield thickness <250 μm (Stratus equivalent) and ≥10% reduction relative to the 24-week study visit at 2 consecutive visits subsequent to the 24-week visit.

eFigure 3. Probability of Chronic Persistent Diabetic Macular Edema Through 2 Years by Treatment Group Among Eyes With Baseline Visual Acuity Letter Score of 68 to 24 (Approximate Snellen Equivalent 20/50 to 20/320)



Weeks	28	32	36	40	44	48	52	68	84	104
Aflibercept										
No. of eyes at risk	31	31	31	28	25	23	23	20	15	15
No. of events	0	0	3	3	2	0	3	4	0	2
Bevacizumab										
No. of eyes at risk	57	57	56	52	51	50	49	42	35	30
No. of events	0	1	4	1	1	1	2	5	3	0
Ranibizumab										
No. of eyes at risk	36	36	36	35	32	32	31	24	20	16
No. of events	0	0	1	3	0	1	5	3	4	1

Time-To-Event Analysis for Resolution of Chronic Persistent DME Adjusted for Baseline Vision and Central Subfield Thickness

Comparison	Hazard Ratio (95% Confidence Interval)	*P*-value
Aflibercept vs. Bevacizumab	1.87 (0.82 to 4.23)	.20
Aflibercept vs. Ranibizumab	1.19 (0.61 to 2.32)	.60
Ranibizumab vs. Bevacizumab	1.56 (0.73 to 3.35)	.37

eFigure 3 Legend: Eyes in which chronic persistent DME did not resolve by 104 weeks were censored on the date of their last visit (N = 64), the date of first non-protocol DME treatment (N = 3), or on the date of the 52-week visit if there were less than 4 visits in year 2 (N = 4). Two-year life-table survival estimates are shown for each group. Solid black = aflibercept, solid gray = bevacizumab, dashed gray = ranibizumab. An event was defined as central subfield thickness <250 μm (Stratus equivalent) and ≥10% reduction relative to the 24-week study visit at 2 consecutive visits subsequent to the 24-week visit.

eTable 1. Persistent Diabetic Macular Edema Through 24 Weeks Stratified by Baseline Visual Acuity

Visit	Baseline Visual Acuity 20/32 to 20/40			Baseline Visual Acuity 20/50 to 20/320		
	Aflibercept[a]	Bevacizumab[b]	Ranibizumab[c]	Aflibercept[d]	Bevacizumab[e]	Ranibizumab[f]
Persistent central-involved DME, No. (%)[g]						
4-Week	66 (67.3)	76 (84.4)	69 (75.8)	67 (74.4)	79 (87.8)	60 (70.6)
8-Week	53 (57.0)	67 (76.1)	60 (67.4)	57 (62.0)	72 (80.0)	50 (59.5)
12-Week	47 (49.5)	65 (73.0)	48 (54.5)	48 (52.2)	64 (72.7)	43 (51.8)
16-Week	42 (43.3)	63 (71.6)	41 (47.1)	40 (44.4)	59 (68.6)	41 (51.3)
20-Week	34 (35.4)	60 (69.0)	41 (46.6)	37 (41.1)	58 (65.2)	37 (44.0)
24-Week[h]	29 (29.6)	61 (67.8)	37 (40.7)	31 (33.7)	57 (63.3)	36 (42.4)

Abbreviations: DME, diabetic macular edema.

[a] N = 98, 93, 95, 97, 96, 98 for the 4-week through 24-week visits, respectively

[b] N = 90, 88, 89, 88, 87, 90 for the 4-week through 24-week visits, respectively

[c] N = 91, 89, 88, 87, 88, 91 for the 4-week through 24-week visits, respectively

[d] N = 90, 92, 92, 90, 90, 92 for the 4-week through 24-week visits, respectively

[e] N = 90, 90, 88, 86, 89, 90 for the 4-week through 24-week visits, respectively

[f] N = 85, 84, 83 ,80, 84, 85 for the 4-week through 24-week visits, respectively

[g] Central-involved DME at each completed study visit. For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 µm for women and ≥320µm for men. For Zeiss Cirrus machines, defined as central subfield thickness ≥290 µm for women and ≥305 µm for men. For Zeiss Stratus machines, defined as central subfield thickness ≥250 µm for both sexes.

[h] Adjusted difference (95% CI, *P*-value) for baseline visual acuity 20/32 to 20/40: bevacizumab-aflibercept = 39.2% (24.0% to 54.4%, <.001), ranibizumab-aflibercept = 7.8% (-5.2% to 20.8%, .24), bevacizumab-ranibizumab = 31.4% (16.5% to 46.4%, <.001); for baseline visual acuity 20/50 to 20/320: bevacizumab-aflibercept = 29.4% (12.7% to 46.2%, <.001), ranibizumab-aflibercept = 8.8% (-5.5% to 23.2%, .23), bevacizumab-ranibizumab = 20.6% (4.1% to 37.1%, .01).

eTable 2. Baseline Participant and Ocular Characteristics by Presence of Persistent Diabetic Macular Edema Through 24 Weeks

	Eyes With Persistent DME Through 24 Weeks			Eyes Without Persistent DME Through 24 Weeks		
	Aflibercept (n = 60)	Bevacizumab (n = 118)	Ranibizumab (n = 73)	Aflibercept (n = 130)	Bevacizumab (n = 62)	Ranibizumab (n = 103)
Female sex, No. (%)	26 (43.3)	54 (45.8)	33 (45.2)	62 (47.7)	31 (50.0)	45 (43.7)
Age, median (IQR), y	62 (55 to 68)	62 (56 to 67)	59 (54 to 67)	60 (53 to 64)	63 (54 to 70)	59 (51 to 65)
Race/Ethnicity, No. (%)						
White	43 (71.7)	77 (65.3)	45 (61.6)	85 (65.4)	41 (66.1)	72 (69.9)
Black/African American	6 (10.0)	19 (16.1)	14 (19.2)	20 (15.4)	6 (9.7)	14 (13.6)
Hispanic or Latino	11 (18.3)	17 (14.4)	13 (17.8)	17 (13.1)	14 (22.6)	14 (13.6)
Asian	0	2 (1.7)	1 (1.4)	2 (1.5)	0	1 (1.0)
Native Hawaiian or other Pacific Islander	0	2 (1.7)	0	2 (1.5)	0	0
More than once race	0	0	0	4 (3.1)	1 (1.6)	1 (1.0)
Unknown or not reported	0	1 (0.8)	0	0	0	1 (1.0)
Diabetes mellitus, No. (%)						
Type 1	8 (13.3)	6 (5.1)	5 (6.8)	12 (9.2)	4 (6.5)	6 (5.8)
Type 2	49 (81.7)	112 (94.9)	65 (89.0)	115 (88.5)	57 (91.9)	94 (91.3)
Uncertain	3 (5.0)	0	3 (4.1)	3 (2.3)	1 (1.6)	3 (2.9)
Duration of diabetes, median (IQR),y	17 (10 to 26)	15 (9 to 23)	17 (13 to 24)	15 (9 to 21)	20 (13 to 28)	16 (11 to 22)
Insulin used, No. (%)	35 (58.3)	75 (63.6)	55 (75.3)	86 (66.2)	45 (72.6)	68 (66.0)
HbA1c, median (IQR), %[a]	7.7 (6.7 to 8.8)	7.7 (6.7 to 8.8)	7.8 (6.8 to 8.7)	7.7 (6.8 to 9.2)	7.6 (6.6 to 8.9)	8.0 (7.0 to 9.6)
Mean arterial pressure, median (IQR), mmHg	102 (91 to 112)	102 (91 to 109)	100 (95 to 106)	100 (90 to 112)	98 (91 to 109)	105 (94 to 113)
Hypertension, No. (%)	49 (81.7)	97 (82.2)	63 (86.3)	100 (76.9)	51 (82.3)	79 (76.7)
Prior PRP, No. (%)	11 (18.3)	24 (20.3)	11 (15.1)	17 (13.1)	13 (21.0)	12 (11.7)
Prior treatment (any type) for DME, No. (%)	34 (56.7)	50 (42.4)	25 (34.2)	44 (33.8)	32 (51.6)	41 (39.8)
Prior laser for DME, No. (%)	30 (50.0)	45 (38.1)	24 (32.9)	40 (30.8)	26 (41.9)	38 (36.9)
Prior intravitreal triamcinolone for DME, No. (%)	5 (8.3)	6 (5.1)	2 (2.7)	5 (3.8)	4 (6.5)	5 (4.9)
Prior vitrectomy for DME, No. (%)	1 (1.7)	0	1 (1.4)	0	1 (1.6)	0
Prior anti-VEGF for DME, No. (%)	8 (13.3)	14 (11.9)	8 (11.0)	13 (10.0)	11 (17.7)	11 (10.7)

	Eyes With Persistent DME Through 24 Weeks			Eyes Without Persistent DME Through 24 Weeks		
	Aflibercept (n = 60)	Bevacizumab (n = 118)	Ranibizumab (n = 73)	Aflibercept (n = 130)	Bevacizumab (n = 62)	Ranibizumab (n = 103)
Lens status (clinical examination), No. (%)						
Phakic	49 (81.7)	89 (75.4)	61 (83.6)	94 (72.3)	43 (69.4)	83 (80.6)
PC IOL	11 (18.3)	29 (24.6)	12 (16.4)	36 (27.7)	19 (30.6)	20 (19.4)
Intraocular pressure, median (IQR), mmHg	16 (14 to 17)	15 (14 to 18)	16 (14 to 17)	15 (13 to 18)	15 (13 to 17)	16 (13 to 18)
Visual acuity						
Letter score, median (IQR)	68 (60 to 74)	69 (59 to 73)	69 (64 to 73)	70 (59 to 74)	68 (62 to 72)	69 (58 to 73)
Approximate Snellen equivalent, median (IQR)	20/50 (20/63 to 20/32)	20/40 (20/63 to 20/40)	20/40 (20/50 to 20/40)	20/40 (20/63 to 20/32)	20/50 (20/63 to 20/40)	20/40 (20/80 to 20/40)
20/32 to 20/40, No. (%)	29 (48.3)	61 (51.7)	37 (50.7)	69 (53.1)	29 (46.8)	54 (52.4)
20/50 to 20/80, No. (%)	21 (35.0)	41 (34.7)	27 (37.0)	37 (28.5)	25 (40.3)	29 (28.2)
20/100 to 20/160, No. (%)	8 (13.3)	14 (11.9)	8 (11.0)	17 (13.1)	5 (8.1)	16 (15.5)
20/200 or worse, No. (%)	2 (3.3)	2 (1.7)	1 (1.4)	7 (5.4)	3 (4.8)	4 (3.9)
OCT machine, No. (%)						
Heidelberg Spectralis	29 (48.3)	57 (48.3)	37 (50.7)	63 (48.5)	32 (51.6)	45 (43.7)
Zeiss Cirrus	26 (43.3)	53 (44.9)	34 (46.6)	62 (47.7)	28 (45.2)	54 (52.4)
Zeiss Stratus	5 (8.3)	8 (6.8)	2 (2.7)	5 (3.8)	2 (3.2)	4 (3.9)
Central subfield thickness, median (IQR), µm	412 (360 to 470)	413 (343 to 511)	427 (363 to 506)	365 (291 to 462)	327 (282 to 428)	355 (295 to 472)
Retinal volume, median (IQR), µL[b]	8.2 (7.7 to 9.9)	8.4 (7.5 to 9.9)	8.7 (7.8 to 10.0)	8.4 (7.5 to 10.3)	8.2 (7.4 to 10.5)	9.0 (7.7 to 9.7)
Epiretinal membrane with center 1 mm deformed, No. (%)[c]	11 (19.6)	29 (25.2)	14 (19.4)	22 (17.2)	21 (33.9)	14 (14.1)
Vitreomacular traction with center 1 mm deformed, No. (%)[c]	9 (16.1)	10 (8.7)	9 (12.5)	16 (12.5)	9 (14.5)	8 (8.1)
Subretinal fluid in central 1 mm, No. (%)[d]	11 (19.3)	36 (31.3)	22 (30.1)	46 (35.9)	16 (25.8)	37 (37.0)
Hemorrhages or microaneurysms within 3 mm of foveal center, No. (%)[e]	50 (84.7)	90 (77.6)	57 (79.2)	108 (83.1)	49 (81.7)	91 (88.3)
Hard exudates within 3 mm of foveal center, No. (%)[f]	49 (83.1)	85 (72.6)	55 (76.4)	99 (76.7)	47 (78.3)	76 (75.2)
Surface wrinkling retinopathy within 3 mm of foveal center, No. (%)[g]	5 (8.6)	7 (6.3)	4 (5.7)	3 (2.4)	3 (5.0)	3 (3.0)

	Eyes With Persistent DME Through 24 Weeks			Eyes Without Persistent DME Through 24 Weeks		
	Aflibercept (n = 60)	Bevacizumab (n = 118)	Ranibizumab (n = 73)	Aflibercept (n = 130)	Bevacizumab (n = 62)	Ranibizumab (n = 103)
Diabetic retinopathy severity on fundus photographs (ETDRS), No. (%)[h]						
Absent or minimal NPDR (levels 10-20)	1 (1.7)	3 (2.6)	0	6 (4.7)	2 (3.3)	2 (1.9)
Mild to moderately severe NPDR (levels 35, 43, 47)	40 (69.0)	77 (66.4)	53 (73.6)	85 (65.9)	31 (51.7)	71 (68.9)
Severe NPDR (level 53)	3 (5.2)	4 (3.4)	3 (4.2)	9 (7.0)	7 (11.7)	12 (11.7)
Prior PRP without current PDR (level 60)	8 (13.8)	13 (11.2)	8 (11.1)	7 (5.4)	7 (11.7)	4 (3.9)
Mild to moderate PDR (levels 61, 65)	6 (10.3)	15 (12.9)	7 (9.7)	20 (15.5)	11 (18.3)	7 (6.8)
High-risk PDR (levels 71, 75)	0	4 (3.4)	1 (1.4)	2 (1.6)	2 (3.3)	7 (6.8)

Abbreviations: DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Severity; NPDR, nonproliferative diabetic retinopathy; OCT, optical coherence tomography; PC IOL, posterior chamber intraocular lens; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor;

[a] HbA1c unavailable for 2 and 3 eyes with and without persistent DME, respectively, treated with aflibercept

[b] Retinal volume unavailable for 9, 19, and 12 eyes with persistent DME and 24, 9, and 16 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups, respectively

[c] Epiretinal membrane and vitreomacular traction data unavailable for 4, 3, and 1 eyes with persistent DME and 2, 0, and 4 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups, respectively

[d] Subretinal fluid data unavailable for 3, 3, and 0 eyes with persistent DME and 2, 0, and 3 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups, respectively

[e] Hemorrhages or microaneurysms data unavailable for 1, 2, and 1 eyes with persistent DME and 0, 2, and 0 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[f] Hard exudates data unavailable for 1, 1, and 1 eyes with persistent DME and 1, 2, and 2 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[g] Surface wrinkling retinopathy data unavailable for 2, 6, and 3 eyes with persistent DME and 3, 2, and 2 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[h] Diabetic retinopathy severity level unavailable for 2, 2, and 1 eyes with persistent DME and 1, 2, and 0 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

eTable 3. Visual Acuity and Optical Coherence Tomography Outcomes at 24 Weeks by Presence of Persistent Diabetic Macular Edema Among Eyes With Baseline Visual Acuity Letter Score of 78 to 69 (Approximate Snellen Equivalent 20/32 to 20/40)

	Eyes With Persistent DME Through 24 Weeks			Eyes Without Persistent DME Through 24 Weeks		
	Aflibercept (n = 29)	Bevacizumab (n = 61)	Ranibizumab (n = 37)	Aflibercept (n = 69)	Bevacizumab (n = 29)	Ranibizumab (n = 54)
Baseline visual acuity						
Letter score, median (IQR)	74 (72 to 76)	73 (70 to 75)	73 (72 to 76)	73 (71 to 75)	73 (70 to 75)	73 (70 to 76)
Approximate Snellen equivalent, median (IQR)	20/32 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/40 (20/40 to 20/32)
24-wk visual acuity						
Letter score, median (IQR)	82 (79 to 84)	80 (76 to 83)	78 (77 to 84)	83 (78 to 86)	79 (76 to 83)	82 (77 to 85)
Approximate Snellen equivalent, median (IQR)	20/25 (20/25 to 20/20)	20/25 (20/32 to 20/25)	20/32 (20/32 to 20/20)	20/25 (20/32 to 20/20)	20/25 (20/32 to 20/25)	20/25 (20/32 to 20/20)
20/25 or better, No. (%)	22 (75.9)	35 (57.4)	18 (48.6)	48 (69.6)	15 (51.7)	39 (72.2)
20/32 to 20/40, No. (%)	6 (20.7)	25 (41.0)	19 (51.4)	20 (29.0)	14 (48.3)	13 (24.1)
20/50 to 20/80, No. (%)	1 (3.4)	1 (1.6)	0	1 (1.4)	0	2 (3.7)
20/100 to 20/160, No. (%)	0	0	0	0	0	0
20/200 or worse, No. (%)	0	0	0	0	0	0
24-wk change in visual acuity letter score from baseline						
Median (IQR)	8 (4 to 11)	6 (3 to 11)	6 (2 to 9)	8 (5 to 13)	5 (3 to 10)	9 (5 to 12)
Mean (SD)[a]	7.2 (6.1)	6.5 (5.6)	5.9 (5.3)	8.6 (6.0)	6.5 (5.7)	8.3 (5.9)
≥15-Letter gain, No. (%)[b]	3 (10.3)	3 (4.9)	2 (5.4)	13 (18.8)	2 (6.9)	6 (11.1)
10-14-Letter gain, No. (%)[b]	9 (31.0)	17 (27.9)	7 (18.9)	21 (30.4)	8 (27.6)	17 (31.5)
5-9-Letter gain, No. (%)	8 (27.6)	18 (29.5)	13 (35.1)	18 (26.1)	6 (20.7)	20 (37.0)
Within ± 4 letters, No. (%)	8 (27.6)	21 (34.4)	15 (40.5)	17 (24.6)	12 (41.4)	9 (16.7)
5-9-Letter loss, No. (%)	0	2 (3.3)	0	0	1 (3.4)	2 (3.7)
10-14-Letter loss, No. (%)[c]	1 (3.4)	0	0	0	0	0
≥15-Letter loss, No. (%)[c]	0	0	0	0	0	0

104-wk change in visual acuity letter score from baseline[d]						
Median (IQR)	6 (2 to 13)	7 (2 to 12)	8 (5 to 13)	10 (4 to 14)	10 (2 to 16)	10 (7 to 14)
Mean (SD)	7.4 (7.0)	7.1 (7.8)	7.5 (8.4)	8.0 (8.9)	8.0 (9.8)	10.4 (5.5)
Change in visual acuity letter score from 24-wk visit to 104-wk visit[d]						
Median (IQR)	0 (-3 to 3)	1 (-4 to 4)	4 (-2 to 7)	-1 (-4 to 4)	2 (-3 to 6)	1 (-2 to 4)
Mean (SD)	0.2 (5.7)	0.9 (6.6)	1.5 (7.8)	-0.6 (7.1)	1.0 (8.9)	1.9 (6.7)
Baseline central subfield thickness, median (IQR), µm	404 (349 to 438)	362 (320 to 427)	413 (353 to 493)	320 (274 to 387)	298 (272 to 364)	328 (287 to 421)
24-wk central subfield thickness, median (IQR), µm	291 (269 to 332)	337 (295 to 379)	311 (270 to 391)	220 (203 to 240)	220 (200 to 247)	228 (199 to 253)
24-wk change in central subfield thickness, median (IQR), µm	-92 (-132 to -62)	-27 (-72 to 4)	-93 (-133 to -24)	-107 (-173 to -55)	-80 (-141 to -26)	-81 (-185 to -56)
Central-Involved DME, No. (%)[e]	29 (100)	61 (100)	37 (100)	6 (8.7)	4 (13.8)	10 (18.5)
Baseline retinal volume, median (IQR), µL[f]	8.0 (7.7 to 9.0)	7.9 (7.3 to 9.0)	8.3 (7.8 to 9.6)	8.0 (7.3 to 9.0)	8.1 (6.9 to 9.6)	8.6 (7.7 to 9.6)
24-wk retinal volume, median (IQR), µL[g]	7.3 (7.1 to 7.9)	7.7 (7.1 to 8.3)	7.9 (7.2 to 8.5)	7.1 (6.8 to 7.4)	7.3 (6.7 to 8.2)	7.2 (6.8 to 7.6)
24-wk change in retinal volume, median (IQR), µL[h]	-0.8 (-1.4 to -0.5)	-0.4 (-0.8 to -0.1)	-0.6 (-1.1 to -0.3)	-1.0 (-1.9 to -0.4)	-0.7 (-1.4 to -0.2)	-1.0 (-1.9 to -0.6)

Abbreviations: DME, diabetic macular edema; OCT, optical coherence tomography.

[a] Adjusted difference (95% CI, *P*-value) for without-with persistent DME: aflibercept = 0.6 (-1.9 to 3.1, .62); bevacizumab = -0.0 (-2.4 to 2.4, .98); ranibizumab = 2.2 (-0.2 to 4.5, .08)

[b] *P*-value for gain ≥10 letters with vs. without persistent DME: aflibercept = .66, bevacizumab = .92, ranibizumab = .09

[c] *P*-value (Fisher's exact test) for lose ≥10 letters with vs. without persistent DME: aflibercept = .30, bevacizumab = 1.00, ranibizumab = 1.00

[d] 104-week visual acuity unavailable for 0, 4, and 2 eyes with persistent DME and 3, 3, and 3 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[e] Central-Involved DME on OCT at the visit. For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 µm for women and ≥320µm for men. For Zeiss Cirrus machines, defined as central subfield thickness ≥290 µm for women and ≥305 µm for men. For Zeiss Stratus machines, defined as central subfield thickness ≥250 µm for both sexes.

[f] Baseline retinal volume unavailable for 4, 7, and 4 eyes with persistent DME and 12, 4, and 5 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[g] 24-week retinal volume unavailable for 1 eye with and 2 eyes without persistent DME in the bevacizumab group

[h] 24-week change in retinal volume unavailable for 4, 8, and 4 eyes with persistent DME and 12, 5, and 5 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

eTable 4. Visual Acuity and Optical Coherence Tomography Outcomes at 24 Weeks by Presence of Persistent Diabetic Macular Edema Among Eyes With Baseline Visual Acuity Letter Score of 68 to 24 (Approximate Snellen Equivalent 20/50 to 20/320)

	Eyes With Persistent DME Through 24 Weeks			Eyes Without Persistent DME Through 24 Weeks		
	Aflibercept (n = 31)	Bevacizumab (n = 57)	Ranibizumab (n = 36)	Aflibercept (n = 61)	Bevacizumab (n = 33)	Ranibizumab (n = 49)
Baseline visual acuity						
Letter score, median (IQR)	60 (51 to 65)	59 (49 to 64)	64 (51 to 67)	58 (48 to 65)	62 (55 to 65)	57 (49 to 63)
Approximate Snellen equivalent, median (IQR)	20/63 (20/100 to 20/50)	20/63 (20/100 to 20/50)	20/63 (20/100 to 20/50)	20/80 (20/125 to 20/50)	20/63 (20/80 to 20/50)	20/80 (20/100 to 20/63)
24-wk visual acuity[a]						
Letter score, median (IQR)	72 (64 to 76)	68 (62 to 76)	72 (59 to 78)	76 (70 to 79)	74 (66 to 76)	73 (65 to 79)
Approximate Snellen equivalent, median (IQR)	20/40 (20/50 to 20/32)	20/50 (20/63 to 20/32)	20/40 (20/80 to 20/32)	20/32 (20/40 to 20/25)	20/32 (20/50 to 20/32)	20/40 (20/50 to 20/25)
20/25 or better, No. (%)	7 (22.6)	12 (21.1)	7 (19.4)	20 (32.8)	4 (12.1)	12 (25.0)
20/32 to 20/40, No. (%)	13 (41.9)	16 (28.1)	14 (38.9)	28 (45.9)	19 (57.6)	16 (33.3)
20/50 to 20/80, No. (%)	7 (22.6)	23 (40.4)	9 (25.0)	10 (16.4)	7 (21.2)	15 (31.3)
20/100 to 20/160, No. (%)	3 (9.7)	4 (7.0)	5 (13.9)	3 (4.9)	3 (9.1)	5 (10.4)
20/200 or worse, No. (%)	1 (3.2)	2 (3.5)	1 (2.8)	0	0	0
24-wk change in visual acuity letter score from baseline[a]						
Median (IQR)	9 (7 to 17)	13 (5 to 18)	10 (5 to 15)	19 (12 to 25)	13 (8 to 18)	17 (11 to 24)
Mean (SD)[b]	12.3 (10.2)	11.3 (10.5)	10.2 (10.4)	18.4 (11.0)	12.3 (9.8)	16.8 (8.5)
≥15-Letter gain, No. (%)[c]	14 (45.2)	21 (36.8)	9 (25.0)	39 (63.9)	12 (36.4)	29 (60.4)
10-14-Letter gain, No. (%)[c]	1 (3.2)	15 (26.3)	9 (25.0)	9 (14.8)	10 (30.3)	10 (20.8)
5-9-Letter gain, No. (%)	11 (35.5)	7 (12.3)	9 (25.0)	7 (11.5)	5 (15.2)	7 (14.6)
Within ± 4 letters, No. (%)	4 (12.9)	11 (19.3)	6 (16.7)	5 (8.2)	3 (9.1)	2 (4.2)
5-9-Letter loss, No. (%)	0	1 (1.8)	2 (5.6)	1 (1.6)	2 (6.1)	0
10-14-Letter loss, No. (%)[d]	1 (3.2)	1 (1.8)	1 (2.8)	0	1 (3.0)	0
≥15-Letter loss, No. (%)[d]	0	1 (1.8)	0	0	0	0

104-wk change in visual acuity letter score from baseline[e]						
Median (IQR)	17 (10 to 24)	14 (5 to 20)	14 (9 to 23)	21 (12 to 28)	15 (9 to 22)	17 (10 to 24)
Mean (SD)	17.0 (11.5)	12.2 (12.5)	16.2 (11.3)	19.8 (14.1)	13.7 (13.8)	16.5 (13.1)
Change in visual acuity letter score from 24-wk visit to 104-wk visit[e]						
Median (IQR)	5 (-2 to 12)	3 (-5 to 7)	5 (-1 to 9)	3 (-1 to 9)	3 (-2 to 6)	1 (-5 to 6)
Mean (SD)	4.7 (11.7)	1.4 (11.6)	5.4 (10.2)	2.4 (9.6)	1.7 (9.6)	0.5 (11.0)
Baseline central subfield thickness, median (IQR), µm	416 (372 to 533)	489 (391 to 571)	438 (374 to 518)	414 (322 to 532)	361 (303 to 481)	389 (318 to 526)
24-wk central subfield thickness, median (IQR), µm[f]	314 (281 to 378)	378 (304 to 482)	338 (292 to 399)	202 (182 to 225)	226 (198 to 236)	209 (180 to 237)
24-wk change in central subfield thickness, median (IQR), µm	-95 (-149 to -67)	-78 (-152 to -33)	-76 (-126 to -17)	-224 (-360 to -116)	-185 (-279 to -78)	-187 (-324 to -121)
Central-Involved DME, No. (%)[g]	31 (100)	57 (100)	36 (100)	1 (1.6)	5 (15.2)	2 (4.1)
Baseline retinal volume, median (IQR), µL[h]	8.8 (7.8 to 10.5)	9.4 (8.2 to 10.7)	8.8 (7.8 to 10.4)	9.2 (7.9 to 11.2)	8.6 (7.7 to 11.9)	9.3 (8.1 to 10.3)
24-wk retinal volume, median (IQR), µL[i]	7.7 (7.0 to 9.1)	9.0 (7.3 to 9.9)	7.8 (7.3 to 8.9)	7.1 (6.6 to 7.8)	7.6 (7.1 to 8.0)	7.1 (6.6 to 7.7)
24-wk change in retinal volume, median (IQR), µL[j]	-1.1 (-1.8 to -0.7)	-0.7 (-1.3 to -0.1)	-0.9 (-1.9 to -0.3)	-2.2 (-3.6 to -0.8)	-1.4 (-3.1 to -0.8)	-2.1 (-4.0 to -1.2)

Abbreviations: DME, diabetic macular edema; OCT, optical coherence tomography.

[a] 24-week visual acuity unavailable for 1 eye without persistent DME in the ranibizumab group

[b] Adjusted difference (95% CI, *P*-value) for without-with persistent DME: aflibercept = 5.3 (1.1 to 9.5, .01); bevacizumab = 1.3 (-2.9 to 5.5, .54); ranibizumab = 5.8 (1.7 to 9.9, .006)

[c] *P*-value for gain ≥10 letters with vs. without persistent DME: aflibercept = .01, bevacizumab = .66, ranibizumab = .01

[d] *P*-value (Fisher's exact test) for lose ≥10 letters with vs. without persistent DME: aflibercept = .34, bevacizumab = 1.00, ranibizumab = .43

[e] 104-week visual acuity unavailable for 0, 6, and 4 eyes with persistent DME and 4, 1, and 2 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[f] For 1 eye in the ranibizumab group with persistent DME that completed the 24-week visit, central subfield thickness was unavailable so the last available (20-week) central subfield thickness measurement was imputed for 24 weeks.

[g] Central-Involved DME on OCT at the visit. For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 µm for women and ≥320µm for men. For Zeiss Cirrus machines, defined as central subfield thickness ≥290 µm for women and ≥305 µm for men. For Zeiss Stratus machines, defined as central subfield thickness ≥250 µm for both sexes.

[h] Baseline retinal volume unavailable for 5, 12, and 8 eyes with persistent DME and 12, 5, and 11 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[i] 24-week retinal volume unavailable for 0, 1, and 1 eyes with persistent DME and 2, 0, and 1 eyes with persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

[j] 24-week change in retinal volume unavailable for 5, 13, and 9 eyes with persistent DME and 14, 5, and 11 eyes without persistent DME in the aflibercept, bevacizumab, and ranibizumab groups

eTable 5. Injections and Laser Treatment by Presence of Chronic Persistent Diabetic Macular Edema

	Eyes With Chronic Persistent DME			Eyes Without Chronic Persistent DME		
	52-Week Visit[a]					
	Aflibercept (n = 47)	Bevacizumab (n = 98)	Ranibizumab (n = 59)	Aflibercept (n = 13)	Bevacizumab (n = 20)	Ranibizumab (n = 14)
No. of injections						
24 wk to before 52-wks						
Median (IQR)	3 (2 to 5)	4 (3 to 6)	4 (3 to 5)	6 (5 to 6)	6 (4 to 7)	6 (4 to 6)
Mean (SD)	3.3 (2.0)	4.0 (2.1)	3.9 (2.0)	4.8 (2.2)	5.3 (2.0)	4.7 (2.2)
Before 52-wks						
Median (IQR)[b]	9 (8 to 11)	10 (8 to 12)	10 (8 to 11)	11 (11 to 12)	12 (10 to 13)	12 (9 to 12)
Mean (SD)	9.3 (2.1)	9.9 (2.1)	9.7 (1.9)	10.8 (2.2)	11.3 (2.1)	10.6 (2.4)
Laser treatment, No. of eyes (%)						
24 wk to before 52-wks[c]	28 (59.6)	68 (69.4)	42 (71.2)	3 (23.1)	12 (60.0)	10 (71.4)
	104-Week Visit[d]					
	Aflibercept (n = 29)	Bevacizumab (n = 70)	Ranibizumab (n = 38)	Aflibercept (n = 30)	Bevacizumab (n = 31)	Ranibizumab (n = 29)
No. of injections						
1 y to before 2 y						
Median (IQR)	5 (3 to 7)	7 (3 to 10)	6 (1 to 9)	3 (2 to 6)	6 (2 to 8)	5 (1 to 8)
Mean (SD)	5.3 (3.4)	6.4 (4.1)	5.2 (4.2)	4.2 (3.9)	6.0 (3.7)	5.3 (4.1)
Before 2 y						
Median (IQR)[e]	15 (12 to 17)	18 (12 to 21)	14 (10 to 19)	14 (10 to 16)	17 (13 to 20)	15 (12 to 21)
Mean (SD)	14.9 (4.9)	16.3 (5.7)	14.6 (5.1)	13.8 (4.7)	17.0 (4.5)	15.8 (5.3)
Laser treatment, No. of eyes (%)						
1 y to before 2 y	9 (31.0)	27 (38.6)	13 (34.2)	7 (23.3)	12 (38.7)	10 (34.5)
Before 2 y[f]	17 (58.6)	52 (74.3)	25 (65.8)	17 (56.7)	25 (80.6)	25 (86.2)
No. of sessions, median (IQR)	1 (0 to 3)	1 (0 to 2)	1 (0 to 2)	1 (0 to 1)	2 (1 to 3)	1 (1 to 2)
No. of sessions, mean (SD)	1.3 (1.5)	1.4 (1.2)	1.2 (1.2)	0.8 (0.8)	1.6 (1.2)	1.5 (1.0)

Abbreviations: DME, diabetic macular edema; IQR, interquartile range; SD, standard deviation.

[a] Includes eyes completing the 52-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, and no non-protocol DME treatment prior to 52 weeks
[b] *P*-value (Wilcoxon rank-sum test) for with vs. without chronic persistent DME: aflibercept = .03, bevacizumab = .004, ranibizumab = .06
[c] *P*-value (Fisher's exact test) for with vs. without chronic persistent DME: aflibercept = .03, bevacizumab = .44, ranibizumab = 1.00
[d] Includes eyes completing the 104-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, at least 4 visits completed in year 2, and no non-protocol DME treatment prior to 104 weeks
[e] *P*-value (Wilcoxon rank-sum test) for with vs. without chronic persistent DME: aflibercept = .38, bevacizumab = .88, ranibizumab = .33
[f] *P*-value (Fisher's exact test) for with vs. without chronic persistent DME: aflibercept = 1.00, bevacizumab = .62, ranibizumab = .09

eTable 6. Injections and Laser Treatment by Presence of Chronic Persistent Diabetic Macular Edema Among Eyes With Baseline Visual Acuity Letter Score 78 to 69 (Approximate Snellen Equivalent 20/32 to 20/40)

	Eyes With Chronic Persistent DME			Eyes Without Chronic Persistent DME		
	52-Week Visit[a]					
	Aflibercept (n = 25)	Bevacizumab (n = 51)	Ranibizumab (n = 29)	Aflibercept (n = 4)	Bevacizumab (n = 10)	Ranibizumab (n = 8)
No. of injections						
24 wks to before 52-wks						
Median (IQR)	2 (1 to 5)	3 (1 to 5)	3 (2 to 5)	6 (3 to 6)	6 (3 to 7)	6 (5 to 7)
Mean (SD)	3.0 (2.1)	3.2 (2.2)	3.7 (2.0)	4.5 (3.0)	4.8 (2.4)	5.4 (1.7)
Before 52-wks						
Median (IQR)[b]	8 (7 to 11)	9 (7 to 11)	9 (8 to 10)	12 (9 to 12)	12 (9 to 13)	12 (10 to 13)
Mean (SD)	8.8 (2.3)	9.1 (2.2)	9.5 (2.0)	10.5 (3.0)	10.8 (2.4)	11.1 (2.1)
Laser treatment, No. of eyes (%)						
24 wks to before 52-wks[c]	14 (56.0)	29 (56.9)	20 (69.0)	1 (25.0)	7 (70.0)	5 (62.5)
	104-Week Visit[d]					
	Aflibercept (n = 16)	Bevacizumab (n = 40)	Ranibizumab (n = 23)	Aflibercept (n = 13)	Bevacizumab (n = 15)	Ranibizumab (n = 12)
No. of injections						
52-wks to before 104-wks						
Median (IQR)	4 (2 to 7)	6 (1 to 9)	5 (1 to 9)	3 (0 to 5)	2 (1 to 6)	2 (0 to 8)
Mean (SD)	4.7 (3.6)	5.3 (4.2)	5.3 (4.3)	3.2 (3.3)	3.7 (3.0)	4.0 (4.2)
Before 104-wks						
Median (IQR) [e]	14 (11 to 17)	15 (9 to 20)	14 (10 to 19)	12 (8 to 15)	14 (12 to 17)	14 (11 to 21)
Mean (SD)	14.0 (5.2)	14.5 (6.0)	14.6 (5.5)	12.0 (3.9)	14.2 (3.5)	14.9 (5.4)
Laser treatment, No. of eyes (%)						
52-wks to before 104-wks	3 (18.8)	12 (30.0)	9 (39.1)	4 (30.8)	3 (20.0)	2 (16.7)
Before 104-wks[f]	7 (43.8)	28 (70.0)	16 (69.6)	9 (69.2)	10 (66.7)	9 (75.0)
No. of sessions, median (IQR)	0 (0 to 1)	1 (0 to 2)	1 (0 to 2)	1 (0 to 1)	1 (0 to 2)	1 (1 to 2)
No. of sessions, mean (SD)	0.8 (1.1)	1.2 (1.1)	1.3 (1.2)	1.0 (0.9)	1.2 (1.3)	1.0 (0.7)

Abbreviations: DME, diabetic macular edema; wks, weeks; IQR, interquartile range; SD, standard deviation.

[a] Includes eyes completing the 52-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, and no non-protocol DME treatment prior to 52 weeks
[b] *P*-value (Wilcoxon rank-sum test) for with vs. without chronic persistent DME: aflibercept = .19, bevacizumab = .03, ranibizumab = .08
[c] *P*-value (Fisher's exact test) for with vs. without chronic persistent DME: aflibercept = .33, bevacizumab = .50, ranibizumab = 1.00
[d] Includes eyes completing the 104-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, at least 4 visits completed in year 2, and no non-protocol DME treatment prior to 104 weeks
[e] *P*-value (Wilcoxon rank-sum test) for with vs. without chronic persistent DME: aflibercept = .32, bevacizumab = .80, ranibizumab = .90
[f] *P*-value (Fisher's exact test) for with vs. without chronic persistent DME: aflibercept = .26, bevacizumab = 1.00, ranibizumab = 1.00

eTable 7. Injections and Laser Treatment by Presence of Chronic Persistent Diabetic Macular Edema Among Eyes With Baseline Visual Acuity Letter Score 68 to 24 (Approximate Snellen Equivalent 20/50 to 20/320)

	Eyes With Chronic Persistent DME			Eyes Without Chronic Persistent DME		
	52-Week Visit[a]					
	Aflibercept (n = 22)	Bevacizumab (n = 47)	Ranibizumab (n = 30)	Aflibercept (n = 9)	Bevacizumab (n = 10)	Ranibizumab (n = 6)
No. of injections						
24 wks to before 52-wks						
Median (IQR)	3 (3 to 5)	5 (4 to 6)	5 (3 to 5)	5 (5 to 6)	7 (5 to 7)	5 (1 to 6)
Mean (SD)	3.7 (1.8)	4.9 (1.6)	4.1 (1.9)	5.0 (1.9)	5.8 (1.5)	3.8 (2.7)
Before 52-wks						
Median (IQR)[b]	9 (9 to 11)	11 (10 to 12)	10 (9 to 11)	11 (11 to 12)	13 (11 to 13)	11 (7 to 12)
Mean (SD)	9.7 (1.8)	10.8 (1.7)	9.9 (1.9)	10.9 (1.9)	11.7 (1.6)	9.8 (2.7)
Laser treatments, No. of eyes (%)						
24 wk to before 52-wks[c]	14 (63.6)	39 (83.0)	22 (73.3)	2 (22.2)	5 (50.0)	5 (83.3)
	104-Week Visit[d]					
	Aflibercept (n = 13)	Bevacizumab (n = 30)	Ranibizumab (n = 15)	Aflibercept (n = 17)	Bevacizumab (n = 16)	Ranibizumab (n = 17)
No. of injections						
52-wks to before 104-wks						
Median (IQR)	6 (4 to 8)	8 (5 to 11)	7 (0 to 9)	3 (2 to 7)	8 (6 to 11)	6 (4 to 8)
Mean (SD)	6.0 (3.0)	7.8 (3.7)	5.2 (4.1)	4.9 (4.2)	8.2 (3.0)	6.2 (4.0)
Before 104-wks						
Median (IQR)[e]	15 (14 to 18)	19 (15 to 22)	16 (10 to 19)	15 (13 to 17)	19 (18 to 23)	16 (13 to 19)
Mean (SD)	15.9 (4.5)	18.7 (4.3)	14.7 (4.7)	15.2 (4.9)	19.6 (3.7)	16.4 (5.3)
Laser treatments, No. of eyes (%)						
52-wks to before 104-wks	6 (46.2)	15 (50.0)	4 (26.7)	3 (17.6)	9 (56.3)	8 (47.1)
Before 104-wks[f]	10 (76.9)	24 (80.0)	9 (60.0)	8 (47.1)	15 (93.8)	16 (94.1)
No. of sessions, median (IQR)	1 (1 to 3)	2 (1 to 3)	1 (0 to 2)	0 (0 to 1)	2 (2 to 3)	2 (1 to 2)
No. of sessions, mean (SD)	2.0 (1.8)	1.7 (1.3)	1.1 (1.3)	0.6 (0.7)	2.1 (0.9)	1.8 (1.0)

Abbreviations: DME, diabetic macular edema; wks, weeks; IQR, interquartile range; SD, standard deviation.

[a] Includes eyes completing the 52-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, and no non-protocol DME treatment prior to 52 weeks
[b] *P*-value (Wilcoxon rank-sum test) for with vs. without chronic persistent DME: aflibercept = .11, bevacizumab = .11, ranibizumab = .75
[c] *P*-value (Fisher's exact test) for with vs. without chronic persistent DME: aflibercept = .05, bevacizumab = .04, ranibizumab = 1.00
[d] Includes eyes completing the 104-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, at least 4 visits completed in year 2, and no non-protocol DME treatment prior to 104 weeks
[e] *P*-value (Wilcoxon rank-sum test) for with vs. without chronic persistent DME: aflibercept = .53, bevacizumab = .58, ranibizumab = .37
[f] *P*-value (Fisher's exact test) for with vs. without chronic persistent DME: aflibercept = .14, bevacizumab = .39, ranibizumab = .03

eTable 8. Visual Acuity and Optical Coherence Tomography Outcomes by Presence of Chronic Persistent Diabetic Macular Edema Among Eyes With Baseline Visual Acuity Letter Score 78 to 69 (Approximate Snellen Equivalent 20/32 to 20/40)

	Eyes With Chronic Persistent DME			Eyes Without Chronic Persistent DME		
	52-Week Visit[a]					
	Aflibercept (n = 25)	Bevacizumab (n = 51)	Ranibizumab (n = 29)	Aflibercept (n = 4)	Bevacizumab (n = 10)	Ranibizumab (n = 8)
Baseline visual acuity, median (IQR)						
Letter score	74 (71 to 76)	73 (70 to 75)	73 (72 to 76)	74 (72 to 77)	74 (71 to 75)	74 (72 to 75)
Approximate Snellen equivalent	20/32 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/32 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/32 (20/40 to 20/32)
Follow-up visual acuity, median (IQR)						
Letter score	82 (79 to 86)	81 (76 to 84)	81 (78 to 84)	84 (81 to 87)	84 (80 to 86)	83 (80 to 85)
Approximate Snellen equivalent	20/25 (20/25 to 20/20)	20/25 (20/32 to 20/20)	20/25 (20/32 to 20/20)	20/20 (20/25 to 20/20)	20/20 (20/25 to 20/20)	20/25 (20/25 to 20/20)
20/25 or better, No. (%)	19 (76.0)	32 (62.7)	20 (69.0)	4 (100)	9 (90.0)	6 (75.0)
20/32 to 20/40, No. (%)	4 (16.0)	18 (35.3)	8 (27.6)	0	1 (10.0)	2 (25.0)
20/50 to 20/80, No. (%)	2 (8.0)	1 (2.0)	1 (3.4)	0	0	0
20/100 to 20/160, No. (%)	0	0	0	0	0	0
20/200 or worse, No. (%)	0	0	0	0	0	0
Change in visual acuity letter score						
Median (IQR)	8 (5 to 11)	8 (4 to 12)	7 (2 to 11)	11 (7 to 12)	10 (9 to 14)	9 (5 to 13)
Mean (SD)[b]	7.4 (7.6)	7.6 (7.0)	6.9 (6.5)	9.3 (4.3)	9.9 (5.9)	9.1 (5.2)
≥15-Letter gain, No. (%)	5 (20.0)	9 (17.6)	4 (13.8)	0	2 (20.0)	1 (12.5)
10-14-Letter gain, No. (%)	4 (16.0)	12 (23.5)	7 (24.1)	3 (75.0)	5 (50.0)	3 (37.5)
5-9-Letter gain, No. (%)	10 (40.0)	11 (21.6)	9 (31.0)	0	2 (20.0)	2 (25.0)
Within ±4 letters, No. (%)	3 (12.0)	16 (31.4)	8 (27.6)	1 (25.0)	0	2 (25.0)
5-9-Letter loss, No. (%)	1 (4.0)	3 (5.9)	1 (3.4)	0	1 (10.0)	0
10-14-Letter loss, No. (%)	2 (8.0)	0	0	0	0	0
≥15-Letter loss, No. (%)	0	0	0	0	0	0
Central-Involved DME, No. (%)[c]	21 (84.0)	48 (94.1)	25 (86.2)	0	3 (30.0)	0

	104-Week Visit[d]					
	Aflibercept (n = 16)	**Bevacizumab (n = 40)**	**Ranibizumab (n = 23)**	**Aflibercept (n = 13)**	**Bevacizumab (n = 15)**	**Ranibizumab (n = 12)**
Baseline visual acuity, median (IQR)						
Letter score	74 (71 to 76)	73 (70 to 75)	73 (72 to 76)	75 (72 to 77)	73 (70 to 75)	74 (72 to 75)
Approximate Snellen equivalent	20/32 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/32 (20/40 to 20/32)	20/40 (20/40 to 20/32)	20/40 (20/40 to 20/32)
Follow-up visual acuity, median (IQR)						
Letter score	80 (77 to 87)	80 (76 to 84)	80 (76 to 84)	84 (78 to 88)	81 (78 to 86)	84 (81 to 86)
Approximate Snellen equivalent	20/25 (20/32 to 20/20)	20/25 (20/32 to 20/20)	20/25 (20/32 to 20/20)	20/20 (20/32 to 20/20)	20/25 (20/32 to 20/20)	20/25 (20/25 to 20/20)
20/25 or better, No. (%)	10 (62.5)	22 (55.0)	14 (60.9)	8 (61.5)	9 (60.0)	11 (91.7)
20/32 to 20/40, No. (%)	6 (37.5)	16 (40.0)	7 (30.4)	5 (38.5)	6 (40.0)	1 (8.3)
20/50 to 20/80, No. (%)	0	2 (5.0)	1 (4.3)	0	0	0
20/100 to 20/160, No. (%)	0	0	1 (4.3)	0	0	0
20/200 or worse, No. (%)	0	0	0	0	0	0
Change in visual acuity letter score						
Median (IQR)	6 (3 to 16)	7 (2 to 11)	8 (1 to 11)	8 (2 to 13)	10 (2 to 13)	11 (7 to 14)
Mean (SD)[e]	7.6 (8.0)	6.8 (7.7)	5.8 (9.4)	7.2 (6.0)	8.0 (7.7)	10.7 (4.9)
≥15-Letter gain, No. (%)[f]	5 (31.3)	5 (12.5)	3 (13.0)	0	2 (13.3)	2 (16.7)
10-14-Letter gain, No. (%)[f]	1 (6.3)	8 (20.0)	5 (21.7)	6 (46.2)	6 (40.0)	5 (41.7)
5-9-Letter gain, No. (%)	3 (18.8)	11 (27.5)	8 (34.8)	2 (15.4)	2 (13.3)	5 (41.7)
Within ±4 letters, No. (%)	6 (37.5)	14 (35.0)	4 (17.4)	5 (38.5)	3 (20.0)	0
5-9-Letter loss, No. (%)	1 (6.3)	1 (2.5)	2 (8.7)	0	2 (13.3)	0
10-14-Letter loss, No. (%)[g]	0	1 (2.5)	0	0	0	0
≥15-Letter loss, No. (%)[g]	0	0	1 (4.3)	0	0	0
Central-Involved DME, No. (%)[c]	15 (93.8)	34 (85.0)	21 (91.3)	0	5 (33.3)	1 (8.3)

Abbreviations: DME, diabetic macular edema; IQR, interquartile range; SD, standard deviation.

[a] Includes eyes completing the 52-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, and no non-protocol DME treatment prior to 52 weeks

[b] Adjusted difference (95% CI, *P*-value) for without-with chronic persistent DME: aflibercept, 2.3 (-5.0 to 9.5, .53); bevacizumab, 2.5 (-1.8 to 6.7, .25); ranibizumab, 1.9 (-3.1 to 6.9, .44)

[c] Central-Involved DME on OCT at the visit. For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 µm for women and ≥320µm for men. For Zeiss Cirrus machines, defined as central subfield thickness ≥290 µm for women and ≥305 µm for men. For Zeiss Stratus machines, defined as central subfield thickness ≥250 µm for both sexes.

[d] Includes eyes completing the 104-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, at least 4 visits completed in year 2, and no non-protocol DME treatment prior to 104 weeks

[e] Adjusted difference (95% CI, *P*-value) for without-with chronic persistent DME: aflibercept = 1.5 (-3.2 to 6.2, .51); bevacizumab = 1.2 (-2.9 to 5.3, .56); ranibizumab = 4.8 (-1.1 to 10.7, .11)
[f] *P*-value for gain ≥10 letters with vs. without chronic persistent DME: aflibercept = .22, bevacizumab = .15, ranibizumab = .16
[g] *P*-value (Fisher's exact test) for lose ≥10 letters with vs. without chronic persistent DME: aflibercept = 1.00, bevacizumab = 1.00, ranibizumab = 1.00

eTable 9. Visual Acuity and OCT Outcomes by Presence of Chronic Persistent Diabetic Macular Edema Among Eyes With Baseline Visual Acuity Letter Score 68 to 24 (Approximate Snellen Equivalent 20/50 to 20/320)

	Eyes With Chronic Persistent DME			Eyes Without Chronic Persistent DME		
	52-Week Visit[a]					
	Aflibercept (n = 22)	Bevacizumab (n = 47)	Ranibizumab (n = 30)	Aflibercept (n = 9)	Bevacizumab (n = 10)	Ranibizumab (n = 6)
Baseline visual acuity, median (IQR)						
Letter score	59 (48 to 65)	59 (49 to 64)	64 (48 to 66)	62 (53 to 65)	57 (53 to 66)	63 (62 to 67)
Approximate Snellen equivalent	20/63 (20/125 to 20/50)	20/63 (20/100 to 20/50)	20/63 (20/125 to 20/50)	20/63 (20/100 to 20/50)	20/80 (20/100 to 20/50)	20/63 (20/63 to 20/50)
Follow-up visual acuity, median (IQR)						
Letter score	74 (66 to 78)	68 (60 to 78)	71 (61 to 77)	76 (74 to 79)	74 (67 to 75)	82 (81 to 83)
Approximate Snellen equivalent	20/32 (20/50 to 20/32)	20/50 (20/63 to 20/32)	20/40 (20/63 to 20/32)	20/32 (20/32 to 20/25)	20/32 (20/50 to 20/32)	20/25 (20/25 to 20/25)
20/25 or better, No. (%)	5 (22.7)	10 (21.3)	6 (20.0)	3 (33.3)	1 (10.0)	5 (83.3)
20/32 to 20/40, No. (%)	10 (45.5)	12 (25.5)	10 (33.3)	5 (55.6)	6 (60.0)	0
20/50 to 20/80, No. (%)	6 (27.3)	17 (36.2)	9 (30.0)	1 (11.1)	2 (20.0)	1 (16.7)
20/100 to 20/160, No. (%)	1 (4.5)	4 (8.5)	4 (13.3)	0	1 (10.0)	0
20/200 or worse, No. (%)	0	4 (8.5)	1 (3.3)	0	0	0
Change in visual acuity letter score						
Median (IQR)	17 (9 to 22)	11 (0 to 18)	10 (3 to 18)	14 (13 to 19)	17 (7 to 21)	18 (13 to 24)
Mean (SD)[b]	17.0 (10.9)	9.2 (12.8)	10.1 (12.8)	16.0 (4.8)	13.4 (8.8)	17.3 (7.9)
≥15-Letter gain, No. (%)	13 (59.1)	15 (31.9)	9 (30.0)	4 (44.4)	6 (60.0)	4 (66.7)
10-14-Letter gain, No. (%)	3 (13.6)	10 (21.3)	6 (20.0)	4 (44.4)	1 (10.0)	1 (16.7)
5-9-Letter gain, No. (%)	2 (9.1)	8 (17.0)	6 (20.0)	1 (11.1)	2 (20.0)	1 (16.7)
Within ±4 letters, No. (%)	4 (18.2)	7 (14.9)	7 (23.3)	0	0	0
5-9-Letter loss, No. (%)	0	3 (6.4)	0	0	1 (10)	0
10-14-Letter loss, No. (%)	0	2 (4.3)	0	0	0	0
≥15-Letter loss, No. (%)	0	2 (4.3)	2 (6.7)	0	0	0
Central-Involved DME, No. (%)[c]	18 (81.8)	46 (97.9)	26 (86.7)	0	5 (50.0)	1 (16.7)

	104-Week Visit[d]					
	Aflibercept (n = 13)	**Bevacizumab (n = 30)**	**Ranibizumab (n = 15)**	**Aflibercept (n = 17)**	**Bevacizumab (n = 16)**	**Ranibizumab (n = 17)**
Baseline visual acuity, median (IQR)						
Letter score	56 (48 to 62)	59 (56 to 65)	64 (41 to 66)	63 (53 to 65)	61 (55 to 65)	62 (54 to 66)
Approximate Snellen equivalent	20/80 (20/125 to 20/63)	20/63 (20/80 to 20/50)	20/50 (20/160 to 20/50)	20/63 (20/100 to 20/50)	20/63 (20/80 to 20/50)	20/63 (20/80 to 20/50)
Follow-up visual acuity, median (IQR)						
Letter score	80 (73 to 87)	73 (68 to 82)	75 (57 to 82)	76 (70 to 79)	72 (67 to 76)	79 (69 to 86)
Approximate Snellen equivalent	20/25 (20/40 to 20/20)	20/40 (20/50 to 20/25)	20/32 (20/80 to 20/25)	20/32 (20/40 to 20/25)	20/40 (20/50 to 20/32)	20/25 (20/40 to 20/20)
20/25 or better, No. (%)	8 (61.5)	12 (40.0)	5 (33.3)	5 (29.4)	2 (12.5)	9 (52.9)
20/32 to 20/40, No. (%)	3 (23.1)	10 (33.3)	3 (20.0)	8 (47.1)	10 (62.5)	5 (29.4)
20/50 to 20/80, No. (%)	2 (15.4)	6 (20.0)	4 (26.7)	2 (11.8)	3 (18.8)	3 (17.6)
20/100 to 20/160, No. (%)	0	1 (3.3)	3 (20.0)	2 (11.8)	1 (6.3)	0
20/200 or worse, No. (%)	0	1 (3.3)	0	0	0	0
Change in visual acuity letter score						
Median (IQR)	21 (21 to 28)	16 (10 to 20)	12 (8 to 21)	13 (10 to 18)	12 (6 to 23)	20 (9 to 23)
Mean (SD)[e]	23.6 (10.3)	14.9 (10.1)	14.7 (13.0)	12.6 (10.1)	13.2 (11.4)	17.5 (9.7)
≥15-Letter gain, No. (%)[f]	10 (76.9)	18 (60.0)	6 (40.0)	7 (41.2)	7 (43.8)	10 (58.8)
10-14-Letter gain, No. (%)[f]	2 (15.4)	5 (16.7)	3 (20.0)	6 (35.3)	2 (12.5)	2 (11.8)
5-9-Letter gain, No. (%)	1 (7.7)	3 (10.0)	4 (26.7)	0	3 (18.8)	4 (23.5)
Within ±4 letters, No. (%)	0	2 (6.7)	2 (13.3)	3 (17.6)	3 (18.8)	1 (5.9)
5-9-Letter loss, No. (%)	0	1 (3.3)	0	0	0	0
10-14-Letter loss, No. (%)[g]	0	1 (3.3)	0	1 (5.9)	1 (6.3)	0
≥15-Letter loss, No. (%)[g]	0	0	0	0	0	0
Central-Involved DME, No. (%)[c]	10 (76.9)	30 (100)	12 (85.7)	2 (11.8)	6 (37.5)	4 (23.5)

Abbreviations: DME, diabetic macular edema; IQR, interquartile range; SD, standard deviation.

[a] Includes eyes completing the 52-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, and no non-protocol DME treatment prior to 52 weeks.

[b] Adjusted difference (95% CI, *P*-value) for without-with chronic persistent DME: aflibercept, 0.6 (-6.5 to 7.6, .87); bevacizumab, 4.2 (-4.4 to 12.8, .33); ranibizumab, 9.2 (-1.9 to 20.2, .10).

[c] Central-Involved DME on OCT at the visit. For Heidelberg Spectralis machines, defined as central subfield thickness ≥305 µm for women and ≥320µm for men. For Zeiss Cirrus machines, defined as central subfield thickness ≥290 µm for women and ≥305 µm for men. For Zeiss Stratus machines, defined as central subfield thickness ≥250 µm for both sexes. 104-week central subfield thickness unavailable for 1 eye in the ranibizumab group with chronic persistent DME.

[d] Includes eyes completing the 104-week visit with DME on OCT at baseline, persistent DME through 24 weeks, 4 injections prior to 24 weeks (or success after 3 injections), 5 of 7 visits completed between weeks 28 and 52, at least 4 visits completed in year 2, and no non-protocol DME treatment prior to 104 weeks.
[e] Adjusted difference (95% CI, *P*-value) for without-with chronic persistent DME: aflibercept = -9.8 (-17.3 to -2.3, .01); bevacizumab = -1.8 (-8.0 to 4.4, .57); ranibizumab = 4.1 (-3.8 to 12.0, .30)
[f] *P*-value for gain ≥10 letters with vs. without chronic persistent DME: aflibercept = .28, bevacizumab = .13, ranibizumab = .63
[g] *P*-value (Fisher's exact test) for lose ≥10 letters with vs. without chronic persistent DME: aflibercept = 1.00, bevacizumab = 1.00, ranibizumab = 1.00