

## Supplemental Online Content

Antoszyk AN, Glassman AR, Beaulieu WT, et al, for the DRCR Retina Network. Effect of intravitreal aflibercept vs vitrectomy with panretinal photocoagulation on visual acuity in patients with vitreous hemorrhage from proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.23027

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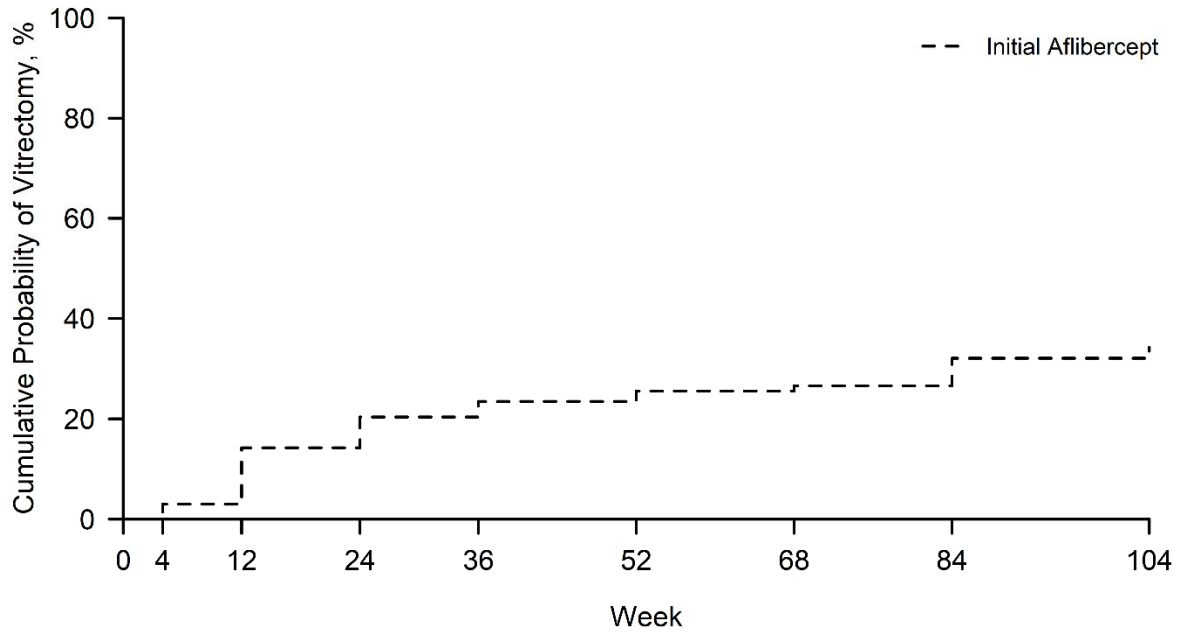
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This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure 1.** Time to First Vitrectomy in the Initial Aflibercept Group: Secondary Outcome

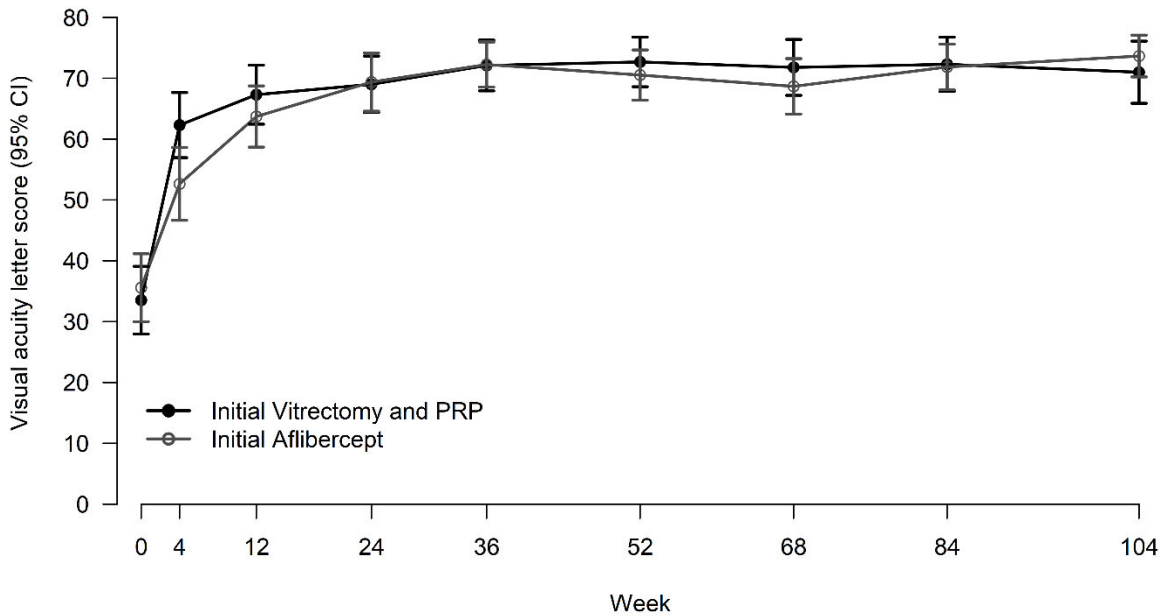


**Number of Eyes at Risk**

Treatment Group	Week							
	0	4	12	24	36	52	68	84
Initial Aflibercept	100	95	84	77	74	71	67	62

**Legend:** At 104 weeks (2 years), the Kaplan-Meier estimate of the cumulative probability was 34% (95% CI, 26% to 45%).

**eFigure 2.** Mean Visual Acuity Letter Score Through 2 Years by Treatment Group

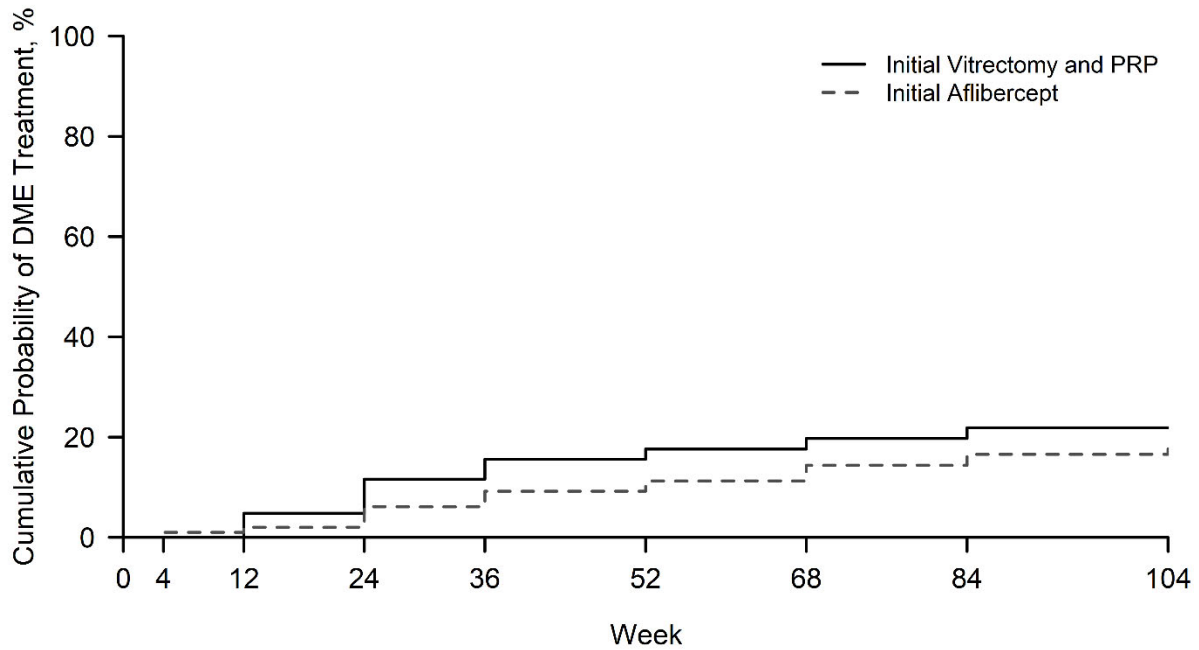


**Number of Observations**

Treatment Group	Week								
	0	4	12	24	36	52	68	84	104
Initial Aflibercept	100	95	97	97	93	95	90	89	90
Initial Vitrectomy and Panretinal Photocoagulation	105	99	102	98	99	98	92	88	87

**Legend:** Error bars represent 95% confidence intervals. Best-corrected visual acuity was collected after protocol-defined refraction. Visual acuity was measured with the Electronic-Early Treatment Diabetic Retinopathy Study visual acuity test on a scale from 100 letters (Snellen equivalent of 20/10) to 0 letters (Snellen equivalent of <20/800); higher scores are better.

**eFigure 3.** Time to First Treatment for Center-Involved Diabetic Macular Edema by Treatment Group: Exploratory Outcome



**Number of Eyes at Risk**

Treatment Group	Week							
	0	4	12	24	36	52	68	84
Initial Vitrectomy and Panretinal Photocoagulation	105	104	98	89	83	78	75	67
Initial Aflibercept	100	97	96	91	88	85	79	75

**Legend:** At 104 weeks (2 years), the Kaplan-Meier estimate of the cumulative probability was 18% (95% CI, 11% to 27%) in the aflibercept group and 22% (95% CI, 15% to 31%) in the vitrectomy group and (all anti-VEGF injections). The hazard ratio comparing the vitrectomy group vs. the aflibercept group, estimated with Cox proportional hazards regression adjusted for baseline lens status as a covariate, was 0.77 (95% CI, 0.41 to 1.46; *P* = .42).

**eTable 1.** Indications for Vitrectomy During Follow-up by Treatment Group

Indication	Treatment Group	
	Initial Aflibercept, No. eyes	Initial Vitrectomy and Panretinal Photocoagulation, <sup>a</sup> No. eyes
<b>First Follow-up Vitrectomy</b>	<b>N = 33</b>	<b>N = 8</b>
Vitreous hemorrhage	22	3
Traction retinal detachment	7	0
Rhegmatogenous retinal detachment	2	2
Endophthalmitis	1	2
Hyphema	0	1
Macular hole	1	0
<b>Second Follow-up Vitrectomy</b>	<b>N = 6</b>	<b>N = 4</b>
Traction retinal detachment	0	1
Rhegmatogenous retinal detachment	4	0
Angle neovascularization	0	1
Choroidal detachment	0	1
Epiretinal membrane	1	0
Macular puckering	0	1
Silicone oil removal	1	0
<b>Third Follow-up Vitrectomy</b>	<b>N = 3</b>	<b>N = 1</b>
Traction retinal detachment	1	1
Rhegmatogenous retinal detachment	1	0
Silicone oil removal	1	0

<sup>a</sup> Excludes the initial randomization vitrectomy.

**eTable 2.** Initial Vitrectomy in the Initial Vitrectomy Group

	<b>Initial Vitrectomy and Panretinal Photocoagulation N = 103<sup>a</sup></b>
Number of unique surgeons	43
Intravitreal aflibercept given before vitrectomy, No. (%)	44 (43)
Surgery time, median (IQR), minutes	30 (25 to 45)
Vitrectomy system gauge, No. (%)	
23	9 (9)
25	92 (89)
27	2 (2)
Intraoperative anti-VEGF used, No. (%) <sup>b</sup>	4 (4)
Intraoperative steroid used, No. (%)	12 (12)
Rhegmatogenous retinal detachment present, No. (%)	
Yes, macula on	1 (<1)
No	102 (>99)
Traction retinal detachment present, No. (%)	
Yes, macula involved	2 (2)
Yes, macula threatened	1 (<1)
Yes, macula not threatened	12 (12)
No	88 (85)
Panretinal photocoagulation performed during surgery, No. (%)	103 (100)
Average power, mean (SD), mW	255 (78)
Exposure time, median (IQR), seconds	0.10 (0.10 to 0.20)
Number of spots, mean (SD)	1012 (505)
Number of quadrants treated, no. (%)	
1	2 (2)
2	9 (9)
3	6 (6)
4	86 (83)
Number of burns with visible effect on retina, mean (SD)	935 (460)
Completed per protocol, No. (%)	102 (99)
Ocular complications during surgery, No. (%)	5 (5)
Retinal tear, No. (%)	4 (4)
Hyphema, No. (%)	1 (1)
Systemic complications during surgery, No. (%) <sup>c</sup>	1 (1)
Staining agent used to visualize epiretinal proliferation, No. (%) <sup>d</sup>	9 (9)
Staining agent used to visualize internal limiting membrane, No. (%) <sup>e</sup>	5 (5)

	<b>Initial Vitrectomy and Panretinal Photocoagulation N = 103<sup>a</sup></b>
Gas placed in the eye, No. (%)	
C <sub>3</sub> F <sub>8</sub>	1 (<1)
Filtered air	32 (31)
SF <sub>6</sub>	2 (2)
Additional procedures performed during surgery, No. (%)	
Cataract extraction	1 (<1)
Cryopexy to retinal tear	0
Fluid-gas exchange	9 (9)
Epiretinal membrane peel	7 (7)
Internal limiting membrane peel	6 (6)
Intraocular lens implantation	1 (<1)
Laser retinopexy to retinal tear	3 (3)
Removal of fibrous proliferation	13 (13)
Scleral buckle	0
Other <sup>f</sup>	6 (6)

Note: Cataract extraction and epiretinal or internal limiting membrane peeling were performed at surgeon discretion.

<sup>a</sup> Two participants assigned to vitrectomy refused surgery and are not included in this table.

<sup>b</sup> Bevacizumab (4).

<sup>c</sup> Oxygen saturation low.

<sup>d</sup> Triamcinolone acetonide (9) and indocyanine green (1).

<sup>e</sup> Indocyanine green (4) and triamcinolone acetonide (2).

<sup>f</sup> Anterior chamber washout (1), fluid-air exchange (2), capsulotomy (1), laser of lattice degeneration (1), and removal of neovascularization from the disc (1).

**eTable 3.** Sensitivity Analyses of Average Visual Acuity Score Over 24 Weeks by Treatment Group, Adjusted for Baseline Visual Acuity and Lens Status

Cohort	Imputation Method <sup>a</sup>	Analysis Method <sup>b</sup>	Adjusted Mean Difference (95% CI), letters <sup>c</sup>	P value
<b>Pre-planned analyses</b>				
Primary analysis: All eyes <sup>d</sup>	Primary analysis: Markov chain Monte Carlo multiple imputation	Primary analysis: Multiple linear regression	-5.0 (-10.2 to 0.3)	.06
All eyes <sup>d</sup>	Predictive mean matching multiple imputation	Multiple linear regression	-5.0 (-10.3 to 0.3)	.06
All eyes <sup>d</sup>	Predictive mean matching multiple imputation	Robust regression using M-estimation	-6.0 (-10.5 to -1.5)	.01
24-week completers <sup>e</sup>	Complete-case analysis	Multiple linear regression	-5.4 (-10.8 to 0.0)	.05
24-week completers <sup>e</sup>	Complete-case analysis	Robust regression using M-estimation	-6.3 (-10.8 to -1.8)	.007
No missed visits through 24 weeks and received all required treatments (per-protocol analysis) <sup>f</sup>	Complete-case analysis	Multiple linear regression	-4.4 (-9.8 to 0.9)	.10
No missed visits through 24 weeks and received all required treatments (per-protocol analysis) <sup>f</sup>	Complete-case analysis	Robust regression using M-estimation	-5.6 (-10.1 to 1.0)	.02
24-week completers <sup>e</sup>	Complete-case analysis	Multiple linear regression with adjustment for additional baseline factors <sup>g</sup>	-3.9 (-9.0 to 1.3)	.14
24-week completers <sup>e</sup>	Complete-case analysis	Robust regression using M-estimation with adjustment for additional baseline factors <sup>g</sup>	-5.3 (-10.0 to -0.6)	.03
24-week completers <sup>e</sup>	Complete-case analysis	Multiple linear regression with Normal score transformation of dependent variable	<sup>h</sup>	.02
All eyes <sup>d</sup>	Markov chain Monte Carlo	Tipping point analysis <sup>i</sup>	<sup>i</sup>	<sup>i</sup>
<b>Post hoc analysis</b>				
All eyes <sup>d</sup>	Markov chain Monte Carlo	Linear mixed effects model with site as a repeated effect	-5.0 (-10.0 to 0.0)	.05



- <sup>a</sup> The primary analysis used the Markov chain Monte Carlo method of multiple imputation, which assumes the data come from a multivariate Normal distribution. Predictive mean matching via the fully conditional specification method of multiple imputation is a nonparametric approach that imputes missing data by imputing observed values from participants with similar covariates. Complete-case analysis uses only observed data and does not carry the distributional assumptions of Markov chain Monte Carlo multiple imputation, but it can be less efficient when data missingness is related to known covariates.
- <sup>b</sup> Multiple linear regression was used for the primary analysis; however, it is sensitive to violations of distributional assumptions such as constant variance (i.e., homoscedasticity) and normality of residuals, which are typically caused by extreme data points (i.e., outliers). Robust regression using M-estimation (with Huber weight function) provides more stable estimates in the presence of outliers. The Normal score transformation (van der Waerden's method) is a nonparametric approach that fits the data to a bell curve, which typically satisfies the distributional assumptions of multiple linear regression; however, a mean difference on the original scale cannot be estimated.
- <sup>c</sup> Positive mean differences indicate better visual acuity score in the aflibercept group (i.e., mean difference = aflibercept – vitrectomy).
- <sup>d</sup> N = 100 for aflibercept and 105 vitrectomy.
- <sup>e</sup> N = 97 for aflibercept and 98 for vitrectomy.
- <sup>f</sup> N = 91 for aflibercept and 94 for vitrectomy.
- <sup>g</sup> Age, diabetes duration, blood pressure, duration of vitreous hemorrhage, hemoglobin A1c, prior panretinal photocoagulation, and prior treatment for diabetic macular edema. This analysis was planned to control for confounding owing to potential imbalance of these factors between treatment groups at baseline. Excludes eyes with missing data for these covariates. N = 94 for aflibercept and 97 for vitrectomy.
- <sup>h</sup> Cannot be estimated on the original scale of letters due to transformation of data.
- <sup>i</sup> A tipping point analysis was performed to test the missing at random assumption of Markov chain Monte Carlo multiple imputation, the method of missing data imputation that was used in the primary analysis. A tipping point of -2 letters was identified for the aflibercept group; i.e., if the missing data in the aflibercept group were truly 2 letters less than the imputed values, then the initial vitrectomy and panretinal photocoagulation group would have been superior to the aflibercept group. There was no biologically plausible tipping point that could be identified to have made the aflibercept group superior to the vitrectomy group. An adjusted difference and *P* value are not provided because the purpose of this analysis is to identify a shift parameter (i.e., the tipping point = -2 letters), not an adjusted difference or *P* value.

**eTable 4.** Subgroup Analyses of Average Visual Acuity Score Over 24 Weeks by Treatment Group, Adjusted for Baseline Visual Acuity and Lens Status

	Treatment Group				Adjusted Mean Difference (95% CI) <sup>a</sup>	Interaction P value
	Initial Aflibercept		Initial Vitrectomy and Panretinal Photocoagulation			
	N	Mean (SD)	N	Mean (SD)		
<b>Prespecified Factors of Primary Interest</b>						
Lens status						
Phakic	72	58.6 (21.3)	76	61.5 (23.3)	-2.9 (-9.2 to 3.3)	.08
Prosthetic intraocular lens	25	61.3 (23.8)	22	68.3 (14.4)	-13.3 (-23.4 to 3.3)	
Prior panretinal photocoagulation						
Yes	41	62.2 (18.6)	54	67.1 (18.3)	-6.4 (-13.3 to 0.6)	.61
No	56	57.2 (23.9)	44	57.9 (24.6)	-3.5 (-12.0 to 5.0)	
Age						
< 60 y	61	60.7 (22.1)	55	61.1 (24.4)	-1.1 (-8.5 to 6.4)	.05 <sup>b</sup>
≥ 60 y	36	56.8 (21.6)	43	65.4 (17.8)	-11.7 (-19.5 to -3.9)	
<b>Prespecified Factors of Secondary Interest</b>						
Prior treatment for diabetic macular edema						
Yes	28	64.2 (20.1)	35	64.5 (20.1)	-3.2 (-11.8 to 5.4)	.62
No	69	57.3 (22.4)	63	62.2 (22.7)	-6.0 (-12.8 to 0.8)	
Prior focal/grid laser for diabetic macular edema <sup>c</sup>						
Yes	15	68.9 (11.2)	15	63.7 (23.5)	NA	
No	82	57.5 (22.9)	83	62.9 (21.6)	NA	

	Treatment Group				Adjusted Mean Difference (95% CI) <sup>a</sup>	Interaction P value
	Initial Aflibercept		Initial Vitrectomy and Panretinal Photocoagulation			
	N	Mean (SD)	N	Mean (SD)		
Prior anti-VEGF for diabetic macular edema						
Yes	22	61.9 (21.5)	28	64.5 (17.9)	-4.3 (-13.1 to 4.6)	.80
No	75	58.5 (22.1)	70	62.4 (23.2)	-5.7 (-12.3 to 0.9)	
Hemoglobin A <sub>1c</sub>						
< 7.5%	30	61.9 (17.0)	34	65.8 (20.1)	-5.5 (-13.2 to 2.2)	.76 <sup>d</sup>
≥ 7.5%	64	59.4 (22.5)	63	61.2 (22.6)	-3.9 (-10.9 to 3.1)	
Duration of vitreous hemorrhage						
< 1 month	57	56.4 (23.7)	53	62.8 (22.0)	-7.8 (-15.2 to -0.3)	.32
≥ 1 month	40	63.3 (18.6)	45	63.2 (21.7)	-2.3 (-10.0 to 5.5)	
Sex						
Female	47	59.2 (24.0)	40	60.1 (23.5)	-3.7 (-12.5 to 5.1)	.61
Male	50	59.3 (20.0)	58	65.0 (20.4)	-6.5 (-13.1 to 0.2)	
Race/Ethnicity						
Non-Hispanic White	35	60.0 (21.1)	43	59.1 (24.7)	-3.2 (-12.8 to 6.4)	.53
Non-White	61	59.5 (22.2)	54	66.0 (19.0)	-6.8 (-13.0 to -0.6)	
Race/Ethnicity <sup>c</sup>						
Hispanic or Latino	42	60.0 (20.1)	40	65.0 (19.0)	NA	
Non-Hispanic White	35	60.0 (21.1)	43	59.1 (24.7)	NA	
Non-Hispanic Black/African American	15	59.3 (27.1)	10	72.7 (8.8)	NA	

<sup>a</sup> Positive mean differences indicate better visual acuity score in the aflibercept group (i.e., mean difference = aflibercept – vitrectomy).

<sup>b</sup> Interaction P value for continuous age = .17

<sup>c</sup> Not analyzed because N < 20 in at least one subgroup.

<sup>d</sup> Interaction P value for continuous Hemoglobin A<sub>1c</sub> = .10

**eTable 5.** Exploratory Visual Acuity Outcomes by Treatment Group

	Treatment Group		Risk Difference, % (95% CI) <sup>a</sup>	P value <sup>a</sup>
	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation		
<b>Change in VA <sup>b</sup> from baseline, adjusted for baseline VA and lens status (exploratory outcome), No. (%)</b>				
<b>4 weeks</b>	<b>N = 95</b>	<b>N = 99</b>		
≥ 30-letter increase <sup>c</sup>	26 (32) [n = 82]	48 (53) [n = 90]		
≥ 15-letter increase	47 (49)	62 (63)	-15 (-30 to -0)	.05
≥ 15-letter decrease <sup>d</sup>	7 (11) [n = 64]	6 (10) [n = 63]	1 (-10 to 13)	.86
≥ 30-letter decrease <sup>e</sup>	4 (7) [n = 57]	5 (9) [n = 53]		
<b>12 weeks</b>	<b>N = 97</b>	<b>N = 102</b>		
≥ 30-letter increase <sup>c</sup>	40 (48) [n = 84]	53 (57) [n = 93]		
≥ 15-letter increase	60 (62)	71 (70)	-7 (-21 to 6)	.29
≥ 15-letter decrease <sup>d</sup>	2 (3) [n = 65]	5 (8) [n = 65]	-5 (-15 to 4)	.28
≥ 30-letter decrease <sup>e</sup>	2 (3) [n = 58]	2 (4) [n = 53]		
<b>24 weeks</b>	<b>N = 97</b>	<b>N = 98</b>		
≥ 30-letter increase <sup>c</sup>	49 (58) [n = 84]	52 (57) [n = 91]		
≥ 15-letter increase	68 (70)	71 (72)	-0 (-12 to 12)	.99
≥ 15-letter decrease <sup>e</sup>	3 (5) [n = 64]	5 (8) [n = 60]	-4 (-14 to 6)	.53
≥ 30-letter decrease <sup>e</sup>	3 (5) [n = 57]	1 (2) [n = 49]		

	Treatment Group		Risk Difference, % (95% CI) <sup>a</sup>	P value <sup>a</sup>
	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation		
<b>1 year</b>	<b>N = 95</b>	<b>N = 98</b>		
≥ 30-letter increase <sup>c</sup>	50 (61) [n = 82]	57 (63) [n = 90]		
≥ 15-letter increase	65 (68)	73 (74)	-3 (-15 to 9)	.59
≥ 15-letter decrease <sup>d</sup>	2 (3) [n = 65]	3 (5) [n = 63]	-2 (-11 to 7)	.71
≥ 30-letter decrease <sup>e</sup>	2 (3) [n = 58]	3 (6) [n = 51]		
<b>2 years</b>	<b>N = 90</b>	<b>N = 87</b>		
≥ 30-letter increase <sup>c</sup>	52 (67) [n=78]	53 (66) [n=80]		
≥ 15-letter increase	68 (76)	65 (75)	2 (-7 to 12)	.63
≥ 15-letter decrease <sup>d</sup>	3 (5) [n=60]	6 (11) [n=53]	-6 (-19 to 4)	.24
≥ 30-letter decrease <sup>e</sup>	2 (4) [n=53]	4 (9) [n=44]		
<b>Distribution of VA letter score, No. (%)</b>				
<b>4 weeks</b>	<b>N = 95</b>	<b>N = 99</b>		
20/20 or better (≥ 84)	8 (8)	12 (12)		
20/25 (79 to 83)	8 (8)	20 (20)		
20/32 to 20/40 (78 to 69)	24 (25)	29 (29)		
20/50 to 20/80 (68 to 54)	22 (23)	14 (14)		
20/100 to 20/160 (53 to 39)	7 (7)	6 (6)		
20/200 to 20/800 (38 to 4)	10 (11)	8 (8)		
Worse than 20/800 (< 3)	16 (17)	10 (10)		

	Treatment Group		Risk Difference, % (95% CI) <sup>a</sup>	P value <sup>a</sup>
	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation		
<b>12 weeks</b>	<b>N = 97</b>	<b>N = 102</b>		
20/20 or better ( $\geq 84$ )	15 (15)	24 (24)		
20/25 (79 to 83)	15 (15)	20 (20)		
20/32 to 20/40 (78 to 69)	30 (31)	29 (28)		
20/50 to 20/80 (68 to 54)	16 (16)	10 (10)		
20/100 to 20/160 (53 to 39)	5 (5)	7 (7)		
20/200 to 20/800 (38 to 4)	9 (9)	5 (5)		
Worse than 20/800 ( $< 3$ )	7 (7)	7 (7)		
<b>24 weeks</b>	<b>N = 97</b>	<b>N = 98</b>		
20/20 or better ( $\geq 84$ )	26 (27)	24 (24)		
20/25 (79 to 83)	16 (16)	14 (14)		
20/32 to 20/40 (78 to 69)	26 (27)	33 (34)		
20/50 to 20/80 (68 to 54)	14 (14)	13 (13)		
20/100 to 20/160 (53 to 39)	5 (5)	4 (4)		
20/200 to 20/800 (38 to 4)	3 (3)	6 (6)		
Worse than 20/800 ( $< 3$ )	7 (7)	4 (4)		
<b>1 year</b>	<b>N = 95</b>	<b>N = 98</b>		
20/20 or better ( $\geq 84$ )	20 (21)	33 (34)		
20/25 (79 to 83)	19 (20)	18 (18)		
20/32 to 20/40 (78 to 69)	32 (34)	25 (26)		
20/50 to 20/80 (68 to 54)	10 (11)	12 (12)		
20/100 to 20/160 (53 to 39)	6 (6)	2 (2)		
20/200 to 20/800 (38 to 4)	4 (4)	6 (6)		
Worse than 20/800 ( $< 3$ )	4 (4)	2 (2)		

	Treatment Group		Risk Difference, % (95% CI) <sup>a</sup>	P value <sup>a</sup>
	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation		
<b>2 years</b>	<b>N = 90</b>	<b>N = 87</b>		
20/20 or better ( $\geq 84$ )	26 (29)	33 (38)		
20/25 (79 to 83)	16 (18)	10 (11)		
20/32 to 20/40 (78 to 69)	20 (22)	23 (26)		
20/50 to 20/80 (68 to 54)	22 (24)	10 (11)		
20/100 to 20/160 (53 to 39)	3 (3)	1 (1)		
20/200 to 20/800 (38 to 4)	2 (2)	6 (7)		
Worse than 20/800 ( $< 3$ )	1 (1)	4 (5)		

Abbreviations: IQR, interquartile range; SD, standard deviation; VA, visual acuity.

<sup>a</sup> For  $\geq 15$ -letter increase, the risk difference and P value were estimated from logistic regression with baseline visual acuity and lens status as covariates following multiple imputation of missing data. For  $\geq 15$ -letter decrease, owing to a low number of events, the exact risk difference was calculated without adjustment for baseline covariates or multiple imputation of missing data and the P value was calculated from Barnard's unconditional exact test. Positive values indicate greater risk with aflibercept (i.e., risk difference = aflibercept – vitrectomy).

<sup>b</sup> Best- corrected visual acuity in the study eye following protocol-defined refraction. Visual acuity was measured with the electronic Early Treatment Study visual acuity test on a scale from 100 letters (Snellen equivalent of 20/10) to 0 letters (Snellen equivalent of  $< 20/800$ )

<sup>c</sup> Includes eyes with baseline visual acuity 70 or lower.

<sup>d</sup> Includes eyes with baseline visual acuity 15 or higher.

<sup>e</sup> Includes eyes with baseline visual acuity 30 or higher.

**eTable 6.** Additional Secondary Visual Acuity Outcomes by Treatment Group

	Treatment Group		Unadjusted Difference (95% CI) <sup>a</sup>	Adjusted Difference (95% CI) <sup>a</sup>	P value <sup>a</sup>
	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation			
<b>12 weeks</b>	<b>N = 97</b>	<b>N = 102</b>			
VA letter score at 12 weeks					
Mean (SD)	63.7 (25.0)	67.3 (24.7)	-4.2 (-11.1 to 2.8)	-4.9 (-11.4 to 1.6)	.14
Mean Snellen equivalent	20/63	20/50			
Median (IQR)	72.0 (80.0 to 57.0)	75.5 (83.0 to 65.0)			
Median Snellen equivalent	20/40	20/32			
20/32 or better (≥ 74), No. (%)	45 (46)	58 (57)	-11 (-25 to 3)	-14 (-28 to 1)	.07
20/200 or worse (≤ 38), No. (%)	16 (16)	12 (12)	6 (-4 to 15)	6 (-3 to 14)	.21
<b>1 year</b>	<b>N = 95</b>	<b>N = 98</b>			
VA letter score at 1 year					
Mean (SD)	70.5 (20.3)	72.7 (20.3)	-2.6 (-8.4 to 3.2)	-3.1 (-8.7 to -2.5)	.28
Mean Snellen equivalent	20/40	20/40			
Median (IQR)	76.0 (83.0 to 68.0)	79.0 (85.0 to 70.0)			
Median Snellen equivalent	20/32	20/25			
20/32 or better (≥ 74), No. (%)	55 (58)	65 (66)	-9 (-23 to 5)	-10 (-24 to 4)	.15
20/200 or worse (≤ 38), No. (%)	8 (8)	8 (8)	1 (-7 to 9)	1 (-6 to 8)	.81

Abbreviations: IQR, interquartile range; Panretinal Photocoagulation, panretinal photocoagulation; SD, standard deviation; VA, visual acuity.

<sup>a</sup> Best-corrected visual acuity in the study eye following protocol-defined refraction. Visual acuity was measured with the electronic Early Treatment Study visual acuity test on a scale from 100 letters (Snellen equivalent of 20/10) to 0 letters (Snellen equivalent of <20/800)

<sup>b</sup> Mean difference estimated via multiple linear regression for continuous outcomes (negative values indicate worse VA score with aflibercept; i.e., aflibercept – vitrectomy) and risk difference estimated via logistic regression and the delta method for binary outcomes (negative values indicate reduced risk with aflibercept; i.e., aflibercept – vitrectomy). No covariate adjustment in the “unadjusted difference” column. Adjusted for baseline VA and lens status as covariates in “adjusted difference” and “P value” columns. Missing data imputed with Markov chain Monte Carlo multiple imputation; the imputation model included treatment group, lens status, baseline VA score, and VA score at common follow-up visits.



**eTable 7.** Proliferative Diabetic Retinopathy Complications by Treatment Group, Adjusted for Baseline Lens Status: Secondary Outcomes

Outcome	Treatment Group		Adjusted Risk Difference, % (95% CI) <sup>a</sup>	P value
	Initial Aflibercept, No. eyes (%)	Initial Vitrectomy and Panretinal Photocoagulation, No. eyes (%)		
Recurrent vitreous hemorrhage at any time <sup>b</sup>	48 (49) [n = 97]	16 (15) [n = 104]	34 (22 to 46)	< .001
Retinal neovascularization on clinical exam <sup>c</sup>				
24 weeks	25 (29) [n = 85]	3 (3) [n = 92]	25 (15 to 36)	< .001
1 year	15 (17) [n = 89]	2 (2) [n = 95]	13 (5 to 21)	.003
2 years	20 (23) [n = 88]	2 (2) [n = 83]	20 (11 to 30)	< .001

<sup>a</sup> Positive values indicate greater risk with aflibercept (i.e., risk difference = aflibercept – vitrectomy).

<sup>b</sup> Assessed by the investigator and defined as presence of vitreous hemorrhage after a period of absence. Excludes eyes in which vitreous hemorrhage could not be assessed during follow-up).

<sup>c</sup> Defined as neovascularization of the disc or elsewhere. Excludes eyes in which retinal neovascularization could not be determined.

**eTable 8.** Retinal Thickening by Treatment Group, Adjusted for Baseline Lens Status: Secondary and Exploratory Outcomes

Outcome	Treatment Group		Adjusted Difference (95% CI) <sup>a</sup>	P value
	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation		
<b>24 weeks</b>	<b>N = 87</b>	<b>N = 90</b>		
Central subfield thickness, mean (SD) <sup>b</sup>	201 (49)	236 (48)	-35 (-50 to -21)	< .001
Center-involved diabetic macular edema, No. (%) <sup>c</sup>	7 (8)	28 (31)	-23 (-34 to -12)	< .001
<b>1 Year</b>	<b>N = 88</b>	<b>N = 94</b>		
Central subfield thickness, mean (SD) <sup>b</sup>	213 (53)	231 (43)	-17 (-32 to -3)	.02
Center-involved diabetic macular edema, No. (%) <sup>c</sup>	15 (17)	27 (29)	-12 (-24 to 1)	.06
<b>2 Years</b>	<b>N = 88</b>	<b>N = 80</b>		
Central subfield thickness, mean (SD) <sup>b</sup>	217 (54)	230 (49)	-13 (-29 to 2)	.09
Center-involved diabetic macular edema, No. (%) <sup>c</sup>	15 (17)	17 (21)	-4 (-16 to 8)	.48

Abbreviations: SD, standard deviation.

<sup>a</sup> Mean difference for continuous outcomes (negative values indicate reduced central subfield thickness with aflibercept; i.e., aflibercept – vitrectomy) and risk difference for binary outcomes (negative values indicate reduced risk of CI-DME with aflibercept; i.e., aflibercept – vitrectomy).

<sup>b</sup> Secondary outcome. Values were converted to Zeiss Stratus equivalents (Bressler SB, Edwards AR, Chalam KV, et al. Reproducibility of Spectral-Domain Optical Coherence Tomography Retinal Thickness Measurements and Conversion to Equivalent Time-Domain Metrics in Diabetic Macular Edema. JAMA Ophthalmol. 2014.)

<sup>c</sup> Exploratory outcome. Defined by OCT central subfield thickness, OCT machine, and participant sex: Zeiss Cirrus ≥ 290 μm in women or ≥ 305 μm in men; Heidelberg Spectralis ≥ 305 μm in women or ≥ 320 μm in men.

**eTable 9.** New and Worsening Retinal Detachments by Treatment Group

Participant No.	Type of RD	First noted on follow-up exam or during vitrectomy?	Days from first injection to first RD	Days from most recent injection to first RD	Number of days from RD to vitrectomy	Macula status <sup>a</sup>	2-Year VA letter score
<b>Initial Vitrectomy and Panretinal Photocoagulation Group</b>							
1	Rhegmatogenous	Follow-up exam			3	Macula on	84
2	Traction	Vitrectomy				Not threatened	84
3 <sup>b</sup>	Traction	Vitrectomy			14	Threatened	91
4	Traction	Vitrectomy				Threatened	87
5	Traction	Vitrectomy				Not threatened	85
6 <sup>b</sup>	Traction	Vitrectomy			56	Involved	23
7	Traction	Vitrectomy				Not threatened	86
8	Traction	Vitrectomy			133	Involved	74
9	Traction	Vitrectomy	3	3		Involved	NA
10	Traction	Vitrectomy	5	5		Not threatened	38
11 <sup>b</sup>	Traction	Vitrectomy	6	6		Not threatened	89
12	Traction	Vitrectomy	13	13		Not threatened	76
13 <sup>b</sup>	Traction	Vitrectomy	13	13	189	Involved	0
14	Traction	Vitrectomy	14	14		Not threatened	86
15	Traction	Follow-up exam	148	148		Not threatened	NA
<b>Initial Aflibercept Group</b>							
16	Rhegmatogenous	Follow-up exam	35	14	6	Macula on	46
17	Traction	Follow-up exam	21	21	18	Involved	65
18	Traction	Follow-up exam	22	22	98	Threatened	79
19	Traction	Follow-up exam	31	31	186	Involved	79
20 <sup>b</sup>	Traction	Vitrectomy	43	13	84	Involved	54
21	Traction	Follow-up exam	52	25	4	Involved	60
22 <sup>b</sup>	Traction	Vitrectomy	55	26	44	Involved	55
23	Traction	Follow-up exam	57	28		Threatened	85
24	Traction	Follow-up exam	61	35	472	Threatened	78
25	Traction	Follow-up exam	94	35	343	Threatened	72
26	Traction	Follow-up exam	111	48		Not threatened	91

Participant No.	Type of RD	First noted on follow-up exam or during vitrectomy?	Days from first injection to first RD	Days from most recent injection to first RD	Number of days from RD to vitrectomy	Macula status <sup>a</sup>	2-Year VA letter score
27	Traction	Follow-up exam	112	28		Not threatened	80
28	Traction	Follow-up exam	115	25	10	Involved	65
29	Traction	Vitrectomy	118	13		Threatened	77
30	Traction	Follow-up exam	123	69		Not threatened	NA
31	Traction	Follow-up exam	140	42	407	Involved	82
32 <sup>b</sup>	Traction	Follow-up exam	161	35	46	Involved	78
33	Traction	Follow-up exam	166	75		Not threatened	86
34	Traction	Follow-up exam	184	126	99	Threatened	NA
35	Traction	Follow-up exam	214	70		Threatened	74
36	Traction	Follow-up exam	446	142		Not threatened	65
37	Traction	Follow-up exam	680	56		Not threatened	68
38	Traction	Vitrectomy	703	27		Not threatened	60

Abbreviations: NA, not available; RD, retinal detachment; VA, visual acuity.

<sup>a</sup> Assessed by investigator and prospectively collected on case report form. For rhegmatogenous RD, options were macula on and macula off. For traction retinal detachment, options were not threatened, threatened, and involved. A traction RD threatening the macula is one that encroaches within 2 disc diameters (approximately 3000 microns) of the foveal center. If the detachment was noted at multiple visits, this column represents the most advanced disease state.

<sup>b</sup> This participant also had a rhegmatogenous RD noted in the study eye at the same visit or later.

**eTable 10.** Systemic Adverse Events by Treatment Group Through 2 Years

No. events (No. participants with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
<b>Blood and lymphatic system disorders</b>		
Anemia	5 (5)	8 (7)
Anemia of chronic disease	1 (1)	1 (1)
Anemia, unspecified	1 (1)	0 (0)
Leukocytosis	1 (1)	1 (1)
Lymphangitis	0 (0)	1 (1)
Neutropenia	1 (1)	0 (0)
Thrombocytopenia	0 (0)	1 (1)
<b>Cardiac disorders</b>		
Acute coronary syndrome	1 (1)	1 (1)
Arteriosclerotic heart disease	1 (1)	0 (0)
Atrial fibrillation	0 (0)	3 (3)
Bicuspid aortic valve	0 (0)	1 (1)
Cardiac arrest	3 (3)	0 (0)
Cardiomegaly	0 (0)	1 (1)
Congestive heart failure	8 (6)	6 (5)
Coronary artery disease	3 (3)	2 (2)
Heart failure	1 (1)	2 (2)
Ischemic cardiomyopathy	1 (1)	0 (0)
Left ventricular hypertrophy	1 (1)	0 (0)
Mitral valve disorders	0 (0)	1 (1)
Mitral valve stenosis	0 (0)	1 (1)
Myocardial disorder	0 (0)	1 (1)
Myocardial infarction	2 (2)	2 (2)
Pericardial effusion	1 (1)	0 (0)
Pulmonary valve regurgitation	1 (1)	0 (0)
Tachycardia	0 (0)	1 (1)
Tricuspid regurgitation	1 (1)	0 (0)
Unstable angina	1 (1)	0 (0)
<b>Congenital, familial and genetic disorders</b>		
Anomaly heart	1 (1)	0 (0)
<b>Ear and labyrinth disorders</b>		
Ear infection	0 (0)	2 (2)
Hearing loss	0 (0)	1 (1)
Otitis externa	0 (0)	1 (1)
Otitis media acute	1 (1)	1 (1)
Tinnitus	0 (0)	1 (1)
Tympanic membrane perforation	1 (1)	0 (0)
<b>Endocrine disorders</b>		
Diabetes	1 (1)	2 (2)
Diabetes mellitus poor control	1 (1)	1 (1)
Diabetic ketoacidosis	7 (4)	3 (2)
Hyperglycemia	2 (2)	2 (2)
Hyperglycemic hyperosmolar nonketotic syndrome	1 (1)	0 (0)

No. events (No. participants with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Hyperparathyroidism	0 (0)	1 (1)
Hypoglycemia	7 (5)	4 (4)
Hypothyroidism	0 (0)	2 (2)
Loss of control of blood sugar	1 (1)	4 (3)
Worsening of diabetes	3 (3)	2 (2)
<b>Gastrointestinal disorders</b>		
Abdominal pain	4 (3)	4 (3)
Acid reflux (oesophageal)	2 (2)	0 (0)
Appendicitis	1 (1)	0 (0)
Barrett's esophagus	1 (1)	0 (0)
Bloody stool	0 (0)	1 (1)
Bowel obstruction	0 (0)	1 (1)
Chipped tooth	2 (2)	0 (0)
Constipation	3 (3)	4 (4)
Diarrhea	8 (6)	1 (1)
Distention	1 (1)	0 (0)
Duodenitis	1 (1)	0 (0)
External hemorrhoids	0 (0)	1 (1)
Food poisoning	0 (0)	1 (1)
Gastric ulcer	0 (0)	1 (1)
Gastritis	2 (2)	0 (0)
Gastroenteritis	6 (4)	0 (0)
Gastroesophageal reflux	2 (2)	2 (2)
Gastroparesis	5 (2)	0 (0)
Hyperemesis	0 (0)	1 (1)
Nausea	5 (5)	7 (7)
Pancreatitis	2 (2)	0 (0)
Peritonitis	1 (1)	0 (0)
Stomach pain	2 (1)	0 (0)
Stomach virus	2 (2)	2 (2)
Tooth abscess	3 (1)	0 (0)
Tooth infection	0 (0)	1 (1)
Toothache	1 (1)	0 (0)
Upset stomach	1 (1)	0 (0)
Vomiting	9 (7)	3 (3)
<b>General disorders and administration site conditions</b>		
Anasarca	1 (1)	0 (0)
Chest pain	4 (4)	2 (2)
Chronic pain	0 (0)	1 (1)
Cyst	1 (1)	1 (1)
Death	2 (2)	1 (1)
Dialysis access malfunction	1 (1)	1 (1)
Fever	1 (1)	2 (2)
Gait disturbance	1 (1)	0 (0)
General Swelling	1 (1)	1 (1)

No. events (No. participants with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Leg edema	5 (4)	2 (2)
Localized superficial swelling, mass, or lump	0 (0)	1 (1)
Pain NOS	0 (0)	1 (1)
Pedal edema	1 (1)	0 (0)
Peripheral edema	1 (1)	0 (0)
Swelling of feet	2 (2)	1 (1)
<b>Hepatobiliary disorders</b>		
Acute cholecystitis	0 (0)	2 (2)
Gallstones	1 (1)	1 (1)
Hepatopathy	1 (1)	0 (0)
Liver enlargement	1 (1)	0 (0)
<b>Immune system disorders</b>		
Allergic reaction	2 (2)	0 (0)
Anaphylaxis	1 (1)	0 (0)
Hives	1 (1)	0 (0)
Seasonal allergy	3 (3)	1 (1)
Specific allergy (drug)	0 (0)	1 (1)
<b>Infections and infestations</b>		
Abscess NOS	0 (0)	3 (3)
Acute pharyngitis	1 (1)	0 (0)
Bacteremia	1 (1)	1 (1)
Diverticulitis	1 (1)	0 (0)
Foot infection	7 (6)	3 (3)
Fungal infection of nail	1 (1)	0 (0)
Fungal skin infection	0 (0)	2 (2)
Gum infection	1 (1)	0 (0)
Infected toe	0 (0)	1 (1)
Infection	1 (1)	4 (2)
Influenza	11 (11)	11 (11)
Lyme disease	0 (0)	1 (1)
MRSA	3 (3)	1 (1)
Sepsis	6 (5)	2 (2)
Streptococcal infection NOS	0 (0)	1 (1)
Thrush	1 (1)	0 (0)
Viral syndrome	0 (0)	1 (1)
Yeast infection	1 (1)	0 (0)
<b>Injury, poisoning and procedural complications</b>		
Back injury	1 (1)	0 (0)
Bug bite	1 (1)	0 (0)
Burn	0 (0)	1 (1)
Fall	10 (9)	4 (4)
Foot injury	2 (2)	0 (0)
Head injury	1 (1)	1 (1)
Knee injury	1 (1)	2 (1)
Laceration of leg	0 (0)	1 (1)
Phlebitis - Injury	1 (1)	0 (0)

No. events (No. participants with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Wound	2 (2)	0 (0)
<b>Investigations</b>		
Blood sugar decreased	1 (1)	1 (1)
Heart rate low	0 (0)	2 (2)
Hormonal imbalance	0 (0)	1 (1)
Intraocular pressure increased	1 (1)	1 (1)
Laboratory test abnormal	1 (1)	2 (1)
Oxygen saturation low	0 (0)	1 (1)
Potassium high	0 (0)	1 (1)
Troponin increased	1 (1)	0 (0)
<b>Metabolism and nutrition disorders</b>		
Abnormal weight gain	0 (0)	1 (1)
Dehydration	3 (3)	1 (1)
Fluid overload - fluid volume increased	3 (2)	1 (1)
Hypercholesterolemia	4 (4)	3 (3)
Hyperkalemia	3 (3)	2 (2)
Hyperlipidemia	1 (1)	1 (1)
Hyperphosphatemia	2 (2)	0 (0)
Hypertriglyceridemia	1 (1)	1 (1)
Hyperuricemia	0 (0)	1 (1)
Hypoalbuminemia	1 (1)	0 (0)
Hypokalemia	0 (0)	2 (2)
Hyponatremia	0 (0)	2 (2)
Iron deficiency	1 (1)	0 (0)
Magnesium deficiency	0 (0)	1 (1)
Malnutrition	0 (0)	1 (1)
Morbid obesity	0 (0)	1 (1)
Type II diabetes mellitus	0 (0)	1 (1)
Vitamin B12 deficiency	1 (1)	0 (0)
Vitamin B6 deficiency	1 (1)	0 (0)
Vitamin D deficiency	1 (1)	0 (0)
Water retention	2 (2)	0 (0)
<b>Musculoskeletal and connective tissue disorders</b>		
Ankle fracture	1 (1)	1 (1)
Arthritis NOS	2 (2)	0 (0)
Back discomfort	2 (2)	0 (0)
Back pain	5 (5)	2 (2)
Back strain	0 (0)	2 (2)
Bone spur	1 (1)	0 (0)
Broken bones	1 (1)	1 (1)
Broken foot	0 (0)	1 (1)
Bunion	0 (0)	1 (1)
Charcot arthropathy	0 (0)	1 (1)
Degenerative disc disease	0 (0)	1 (1)
Dislocated shoulder	0 (0)	1 (1)
Femur fracture	1 (1)	0 (0)



No. events (No. participants with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Foot fracture	0 (0)	1 (1)
Foot pain	2 (1)	0 (0)
Fractured collar bone	0 (0)	1 (1)
Fractured ribs	1 (1)	1 (1)
Frozen shoulder	0 (0)	1 (1)
Generalized muscle weakness	1 (1)	1 (1)
Gout	1 (1)	3 (3)
Hand pain	0 (0)	1 (1)
Hip fracture	2 (2)	2 (1)
Intervertebral disc bulging	1 (1)	0 (0)
Knee pain	4 (4)	1 (1)
Leg pain	2 (2)	1 (1)
Muscle cramps	3 (2)	0 (0)
Muscle pain	3 (3)	2 (2)
Muscle spasms	0 (0)	1 (1)
Neck pain	1 (1)	0 (0)
Osteomyelitis	8 (5)	1 (1)
Pain in arm	1 (1)	0 (0)
Pain in hip	1 (1)	1 (1)
Pulled hamstring	1 (1)	0 (0)
Scoliosis	1 (1)	0 (0)
Shoulder pain	2 (2)	2 (2)
Sprained ankle	1 (1)	0 (0)
Sprains and strains of ribs	1 (1)	1 (1)
Wrist fracture	1 (1)	1 (1)
Wrist pain	1 (1)	0 (0)
<b>Nervous system disorders</b>		
Bell's palsy	0 (0)	1 (1)
Carpal tunnel syndrome	0 (0)	2 (2)
Coma	1 (1)	0 (0)
Concussion	0 (0)	1 (1)
Diabetic neuropathy	1 (1)	0 (0)
Dizziness	4 (4)	3 (3)
Head pain	2 (2)	0 (0)
Head pressure	1 (1)	0 (0)
Headache	9 (9)	7 (7)
Migraine headache	4 (3)	0 (0)
Neuropathy	4 (4)	0 (0)
Numbness in hand	0 (0)	1 (1)
Paralysis	0 (0)	1 (1)
Restless leg syndrome	1 (1)	0 (0)
Sciatica	2 (2)	0 (0)
Seizures	1 (1)	0 (0)
Syncope	1 (1)	1 (1)
Vlth nerve palsy	0 (0)	1 (1)
Vertigo	1 (1)	4 (4)

No. events (No. participants with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Viral meningitis	0 (0)	1 (1)
<b>Psychiatric disorders</b>		
Adjustment disorder NOS	1 (1)	0 (0)
Anxiety	4 (4)	1 (1)
Depression	2 (2)	3 (3)
Drug abuse	1 (1)	0 (0)
Insomnia	0 (0)	1 (1)
Post-traumatic stress disorder	1 (1)	0 (0)
<b>Renal and urinary disorders</b>		
Acute kidney injury	3 (3)	4 (3)
Acute renal failure	1 (1)	1 (1)
Bladder infection	1 (1)	1 (1)
Chronic kidney disease	5 (3)	8 (7)
Chronic renal failure worsened	1 (1)	4 (3)
End stage renal disease (ESRD)	2 (2)	1 (1)
Hydronephrosis	0 (0)	1 (1)
Kidney failure	8 (8)	4 (3)
Kidney function abnormal	2 (2)	0 (0)
Kidney infection	3 (2)	1 (1)
Kidney stones	3 (3)	1 (1)
Nephrotic syndrome	1 (1)	0 (0)
Nocturia	1 (1)	0 (0)
Proteinuria	1 (1)	0 (0)
Pyelonephritis	0 (0)	1 (1)
Renal failure	2 (2)	1 (1)
Renal insufficiency	0 (0)	1 (1)
Uremia	1 (1)	0 (0)
Urinary hesitancy	0 (0)	1 (1)
Urinary incontinence	0 (0)	1 (1)
Urinary tract infection	14 (9)	9 (7)
<b>Reproductive system and breast disorders</b>		
Enlarged prostate	1 (1)	0 (0)
Erectile dysfunction	2 (2)	1 (1)
Hydrocele	0 (0)	1 (1)
Testicular torsion	0 (0)	1 (1)
Uterine bleeding	1 (1)	0 (0)
Uterine fibroid	1 (1)	0 (0)
Vulvodynia	0 (0)	1 (1)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Acute bronchitis	4 (4)	0 (0)
Acute respiratory failure	2 (2)	1 (1)
Acute sinusitis	1 (1)	1 (1)
Allergic rhinitis	3 (3)	1 (1)
Asthma	1 (1)	0 (0)
Bronchitis	6 (6)	1 (1)
Bronchospasm	1 (1)	0 (0)

No. events (No. participants with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Cardiopulmonary arrest	1 (1)	0 (0)
Chest congestion	0 (0)	1 (1)
Cold	17 (13)	9 (7)
Cough	1 (1)	2 (2)
Dyspnea	1 (1)	2 (2)
Epistaxis	0 (0)	1 (1)
Exacerbation of asthma	0 (0)	2 (1)
Hypoxemia	1 (1)	1 (1)
Nasal congestion	1 (1)	0 (0)
Pleural effusion	1 (1)	2 (2)
Pneumonia	4 (4)	7 (6)
Pulmonary edema	2 (2)	0 (0)
Pulmonary embolism	1 (1)	0 (0)
Respiratory distress	0 (0)	1 (1)
Shortness of breath	12 (10)	4 (4)
Sinus infection	4 (4)	1 (1)
Sinusitis	1 (1)	3 (3)
Sleep apnea	0 (0)	1 (1)
Upper respiratory infection	4 (3)	4 (3)
Wheezing	0 (0)	1 (1)
<b>Skin and subcutaneous tissue disorders</b>		
Blister of foot and toe(s), without mention of infection	2 (2)	1 (1)
Bruise	0 (0)	1 (1)
Cellulitis	2 (1)	2 (2)
Cellulitis of arm	2 (1)	0 (0)
Cellulitis of foot	1 (1)	2 (2)
Cellulitis of leg	1 (1)	0 (0)
Cellulitis of toe	2 (2)	0 (0)
Decubitus ulcer	0 (0)	1 (1)
Diabetic foot ulcer	3 (3)	3 (2)
Diabetic ulcer	1 (1)	0 (0)
Epidermal cyst	1 (1)	0 (0)
Erythematous conditions	1 (1)	0 (0)
Foot ulcer	3 (2)	6 (4)
Fungal infection of nail	0 (0)	1 (1)
Itching	1 (1)	0 (0)
Mole of skin	1 (1)	0 (0)
Rash	2 (2)	1 (1)
Sebaceous cyst	1 (1)	0 (0)
Skin abrasion	1 (1)	0 (0)
Skin cancer	0 (0)	1 (1)
Skin infection	3 (3)	0 (0)
Swelling of face	1 (1)	0 (0)
<b>Surgical and medical procedures</b>		
Back surgery	0 (0)	1 (1)
Benign tumor excision	1 (1)	1 (1)

No. events (No. participants with $\geq 1$ event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Bypass surgery	0 (0)	1 (1)
Carpal tunnel release	1 (1)	0 (0)
Coronary artery bypass graft	1 (1)	0 (0)
Coronary stent placement	0 (0)	1 (1)
Foot surgery	2 (2)	1 (1)
Implantable defibrillator insertion	1 (1)	1 (1)
Knee surgery NOS	0 (0)	1 (1)
Metatarsal excision	1 (1)	0 (0)
Sinus operation	1 (1)	0 (0)
Skin graft	18 (1)	0 (0)
Stent placement	0 (0)	2 (2)
Surgery	2 (2)	3 (2)
Toe amputation	0 (0)	4 (4)
Tooth extraction	3 (3)	3 (3)
Wrist surgery	0 (0)	1 (1)
<b>Vascular disorders</b>		
Arteriovenous graft site hemorrhage	0 (0)	1 (1)
Benign essential hypertension	1 (1)	0 (0)
Deep vein thrombosis	1 (1)	1 (1)
Embolism - blood clot	2 (2)	0 (0)
Hypertension	4 (4)	6 (6)
Hypertension worsened	11 (9)	5 (5)
Hypertensive crisis	2 (2)	1 (1)
Hypotension	6 (4)	2 (2)
Iliac artery blockage	0 (0)	1 (1)
Intraventricular hemorrhage	0 (0)	1 (1)
Ischemia - systemic	0 (0)	1 (1)
Peripheral arterial disease	0 (0)	1 (1)
Peripheral vascular disease	1 (1)	0 (0)
Stroke	1 (1)	1 (1)
Stroke (cerebrovascular accident)	0 (0)	1 (1)
Stroke - Ischemic	1 (1)	0 (0)
Transient ischemic attacks	0 (0)	1 (1)

**eTable 11.** Ocular Adverse Events Occurring in Study Eyes by Treatment Group Through 2 Years

No. events (No. eyes with $\geq 1$ event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
<b>Anterior chamber</b>		
Anterior chamber angle neovascularisation	3 (3)	1 (1)
Anterior chamber cell	4 (4)	4 (3)
Hyphema	0 (0)	5 (4)
<b>Cataract</b>		
Cataract fragments in eye postoperative	0 (0)	1 (1)
<b>Choroid</b>		
Choroidal detachment	0 (0)	2 (2)
<b>Conjunctiva</b>		
Allergic conjunctivitis	0 (0)	1 (1)
Conjunctival cyst	0 (0)	1 (1)
Conjunctival hyperemia	0 (0)	2 (1)
Foreign body in conjunctival sac	0 (0)	2 (2)
Red eye	2 (1)	0 (0)
Subconjunctival hemorrhage	3 (3)	4 (4)
Subconjunctival/conjunctival hemorrhage	0 (0)	1 (1)
<b>Cornea</b>		
Band keratopathy	0 (0)	1 (1)
Corneal abrasion	3 (3)	2 (2)
Corneal defect	1 (1)	1 (1)
Corneal disorder (NOS)	0 (0)	1 (1)
Corneal edema	0 (0)	5 (5)
Corneal endothelial disorder	1 (1)	0 (0)
Corneal erosion	0 (0)	1 (1)
Corneal guttata	0 (0)	1 (1)
Corneal haze	0 (0)	1 (1)
Corneal irritation	0 (0)	2 (2)
Corneal scar	0 (0)	1 (1)
Corneal ulcer	0 (0)	2 (2)
Exposure keratoconjunctivitis	0 (0)	2 (1)
Folds in Descemet's membrane	0 (0)	1 (1)
Keratopathy NOS	0 (0)	1 (1)
Punctate epithelial erosion	3 (3)	0 (0)
Superficial punctate keratitis	3 (3)	2 (2)
<b>External</b>		
Bee sting	0 (0)	1 (1)
Black eye	0 (0)	1 (1)
Dry eye	6 (6)	7 (7)
Dry eye syndrome	1 (1)	1 (1)
Eye irritation	2 (2)	5 (5)
Eye tearing	2 (2)	1 (1)
Swollen eyes	2 (2)	0 (0)
Watering eyes	1 (1)	2 (2)

No. events (No. eyes with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
<b>Glaucoma-IOP</b>		
Glaucoma	2 (2)	5 (4)
Hypotony of eye	0 (0)	1 (1)
Intraocular pressure increased	6 (6)	9 (8)
Neovascular glaucoma	1 (1)	2 (2)
Ocular hypertension	3 (3)	3 (3)
<b>Inflammation</b>		
Anterior chamber flare	2 (2)	2 (2)
Iritis (anterior uveitis, iridocyclitis)	2 (1)	1 (1)
<b>Iris</b>		
Iris neovascularization	2 (2)	2 (2)
Rubeosis iridis	0 (0)	3 (3)
Synechiae	1 (1)	0 (0)
<b>Lens</b>		
Cataract	14 (14)	23 (20)
Cataract cortical	5 (5)	2 (1)
Cataract extraction	2 (2)	1 (1)
Cataract subcapsular	1 (1)	1 (1)
Cortical spoking	7 (7)	2 (2)
Deposit on the surface of intraocular lens	1 (1)	0 (0)
Nuclear sclerosis	16 (15)	10 (10)
Posterior capsule opacification	11 (10)	12 (11)
Posterior subcapsular cataract	19 (16)	19 (16)
Secondary cataract	1 (1)	0 (0)
Senile nuclear sclerosis	0 (0)	1 (1)
<b>Lids</b>		
Blepharitis (eyelid irritation)	1 (1)	2 (2)
Chalazion	0 (0)	1 (1)
Eyelid edema	0 (0)	1 (1)
Eyelid twitching	0 (0)	1 (1)
Hordeolum	1 (1)	0 (0)
Meibomian gland obstruction	0 (0)	1 (1)
Ptosis	0 (0)	2 (2)
Stye	0 (0)	1 (1)
Swollen eyelid	1 (1)	0 (0)
<b>Miscellaneous-eye</b>		
Eye injury	1 (1)	0 (0)
Eye strain	1 (1)	0 (0)
Vlth nerve palsy	0 (0)	1 (1)
<b>Miscellaneous-systemic</b>		
Venous malformation NOS	1 (1)	1 (1)
<b>Optic nerve</b>		
Cupping of optic nerve	0 (0)	1 (1)
Optic nerve pallor	2 (2)	0 (0)
<b>Retina</b>		
Atrophy of macula	0 (0)	1 (1)

No. events (No. eyes with $\geq 1$ event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
Detachment of retinal pigment epithelium	0 (0)	1 (1)
Diabetic macular edema	11 (10)	11 (9)
Disc neovascularization	7 (7)	0 (0)
Epiretinal membrane	13 (12)	13 (13)
Flame-shaped hemorrhage	1 (1)	0 (0)
Hypertensive retinopathy	1 (1)	1 (1)
Intraretinal microvascular abnormalities	4 (2)	0 (0)
Ischemia retinal	0 (0)	2 (2)
Lattice degeneration of retina	1 (1)	0 (0)
Macular atrophy	1 (1)	0 (0)
Macular dystrophy	0 (0)	1 (1)
Macular edema	0 (0)	1 (1)
Macular hole	2 (2)	0 (0)
Macular puckering	1 (1)	2 (2)
Macular scar	0 (0)	1 (1)
Neurosensory detachment	0 (0)	1 (1)
Ocular fundus arteriosclerosis	0 (0)	1 (1)
Preretinal fibrosis	2 (2)	0 (0)
Preretinal hemorrhage	3 (3)	0 (0)
Proliferative vitreoretinopathy	1 (1)	0 (0)
Retinal cyst	0 (0)	1 (1)
Retinal edema	1 (1)	2 (2)
Retinal exudates	5 (4)	3 (3)
Retinal hemorrhage	1 (1)	0 (0)
Retinal macroaneurysm	1 (1)	0 (0)
Retinal neovascularization	9 (7)	3 (3)
Retinal tear	7 (7)	5 (5)
Retinal vessel avulsion	2 (2)	0 (0)
Rhegmatogenous retinal detachment	5 (4)	5 (5)
Subretinal fibrosis	0 (0)	1 (1)
Subretinal hemorrhage	1 (1)	0 (0)
Traction retinal detachment	26 (22)	15 (14)
Varying retinal vessel calibre	1 (1)	0 (0)
Vitreoretinal traction syndrome	1 (1)	0 (0)
<b>Sensation-pain</b>		
Eye ache	1 (1)	1 (1)
Eye itching	5 (3)	7 (7)
Eye pain	14 (11)	7 (6)
Eyelid pain	1 (1)	0 (0)
Foreign body sensation in eyes	2 (2)	4 (4)
Ocular discomfort	2 (2)	0 (0)
Sensation of pressure in eye	0 (0)	1 (1)
Soreness in eyes	5 (3)	0 (0)
<b>Skin</b>		
Dermatochalasis	0 (0)	2 (2)
Skin lesion	0 (0)	1 (1)

No. events (No. eyes with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
<b>Visual field</b>		
Vision peripheral decreased	0 (0)	1 (1)
<b>Visual symptoms/abnormality</b>		
Amaurosis fugax	1 (1)	0 (0)
Blurred vision	10 (9)	3 (3)
Blurry vision	11 (10)	3 (3)
Cloudy vision	0 (0)	4 (4)
Decrease in depth perception	1 (1)	0 (0)
Diplopia	0 (0)	1 (1)
Double vision	2 (2)	2 (2)
Filmy vision	1 (1)	0 (0)
Glare	0 (0)	1 (1)
Hazy vision	4 (4)	1 (1)
Photophobia	3 (3)	1 (1)
Photopsia	1 (1)	1 (1)
Sensitivity to light (photophobia)	2 (2)	4 (4)
Vision decreased	11 (11)	6 (5)
Visual acuity decreased	5 (4)	1 (1)
Visual disturbances	2 (2)	1 (1)
Visual flashes	5 (3)	5 (5)
<b>Vitreous</b>		
Endophthalmitis	1 (1)	2 (2)
Floaters	30 (24)	11 (11)
Posterior vitreous detachment	2 (2)	0 (0)
Vitrectomy	1 (1)	0 (0)
Vitreous debris	3 (3)	0 (0)
Vitreous disorder NOS	1 (1)	0 (0)
Vitreous floater	2 (2)	0 (0)
Vitreous hemorrhage	77 (52)	31 (24)
Vitreous membranes and strands	0 (0)	1 (1)
Vitreous opacities	1 (1)	0 (0)
Vitreous opacity	1 (1)	0 (0)



**eTable 12.** Ocular Adverse Events Occurring in Non-Study Eyes After the First Non-Study Eye Aflibercept Injection by Treatment Group Through 2 Years

No. events (No. eyes with ≥1 event)	Initial Aflibercept	Initial Vitrectomy and Panretinal Photocoagulation
<b>Conjunctiva</b>		
Conjunctival hyperemia	0 (0)	1 (1)
Subconjunctival hemorrhage	0 (0)	1 (1)
<b>Cornea</b>		
Corneal abrasion	1 (1)	0 (0)
<b>External</b>		
Black eye	0 (0)	1 (1)
Dry eye	0 (0)	1 (1)
Watering eyes	1 (1)	1 (1)
<b>Glaucoma-IOP</b>		
Intraocular pressure increased	0 (0)	1 (1)
<b>Lens</b>		
Cataract subcapsular	0 (0)	1 (1)
Posterior capsule opacification	0 (0)	1 (1)
Posterior subcapsular cataract	0 (0)	2 (2)
<b>Lids</b>		
Blepharitis (eyelid irritation)	0 (0)	1 (1)
Ptosis	0 (0)	1 (1)
<b>Retina</b>		
Diabetic macular edema	0 (0)	2 (2)
Epiretinal membrane	0 (0)	3 (3)
Macular edema	0 (0)	1 (1)
Retinal exudates	0 (0)	1 (1)
Retinal tear	0 (0)	1 (1)
<b>Sensation-pain</b>		
Eye ache	0 (0)	1 (1)
Eye itching	1 (1)	0 (0)
Eye pain	1 (1)	1 (1)
Foreign body sensation in eyes	0 (0)	1 (1)
<b>Skin</b>		
Dermatochalasis	0 (0)	1 (1)
<b>Visual symptoms/abnormality</b>		
Blurry vision	1 (1)	0 (0)
Sensitivity to light (photophobia)	0 (0)	1 (1)
Vision decreased	0 (0)	1 (1)
<b>Vitreous</b>		
Endophthalmitis	0 (0)	1 (1)
Vitreous hemorrhage	1 (1)	9 (8)