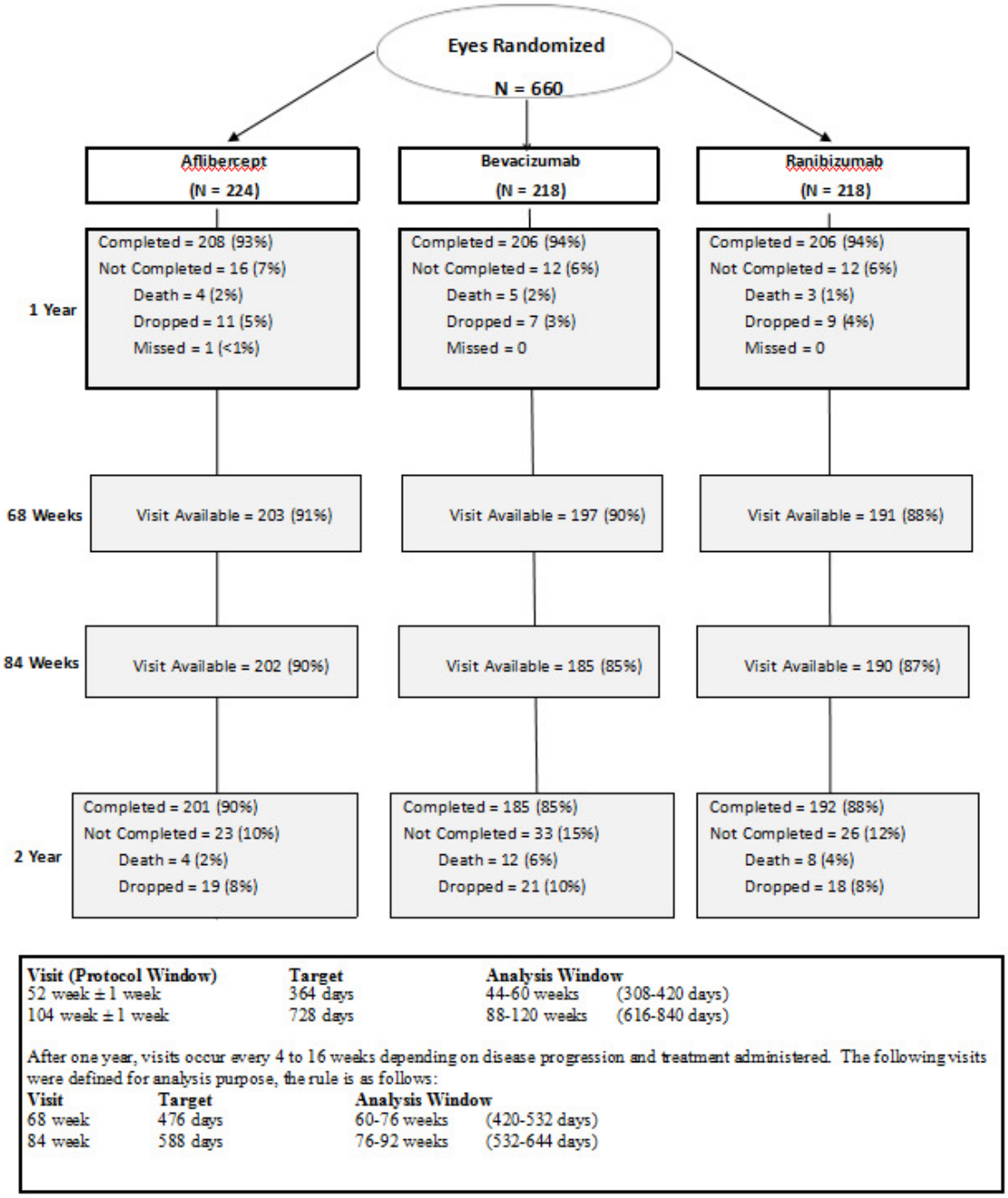
Contents

Figure S1. Completion of Follow-up



Visit (Protocol Window)	Target	Analysis Window	
52 week ± 1 week	364 days	44-60 weeks	(308-420 days)
104 week ± 1 week	728 days	88-120 weeks	(616-840 days)

After one year, visits occur every 4 to 16 weeks depending on disease progression and treatment administered. The following visits were defined for analysis purpose, the rule is as follows:

Visit	Target	Analysis Window	
68 week	476 days	60-76 weeks	(420-532 days)
84 week	588 days	76-92 weeks	(532-644 days)

Note: 13 patients dropped prior to 2 year but had a Post 52wk in analysis window counted as a "Completed" 2 year in A=2, B=4, R=7. 1 A, 1 B, and 3 R were deaths, so the number of deaths in the AE tables will be this many more than the number in the flow chart.

Figure S2. Change in Visual Acuity from Baseline to 2 Year by Treatment Group According to Baseline Visual Acuity

Figure S2A

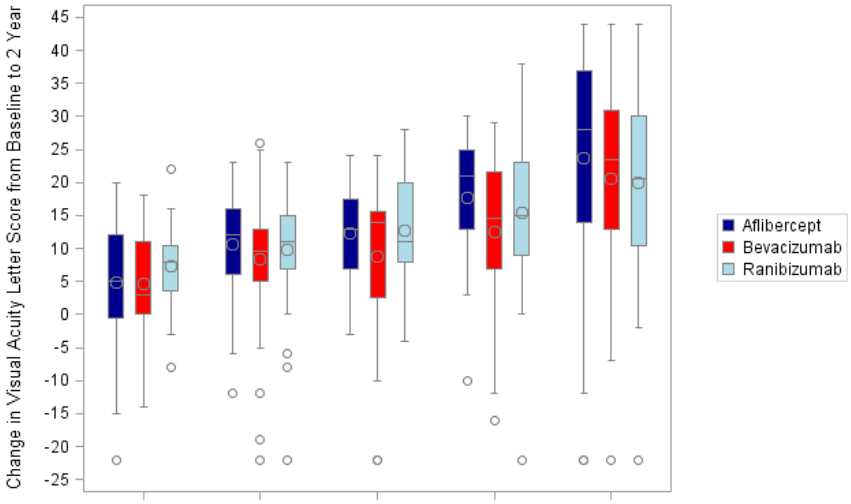
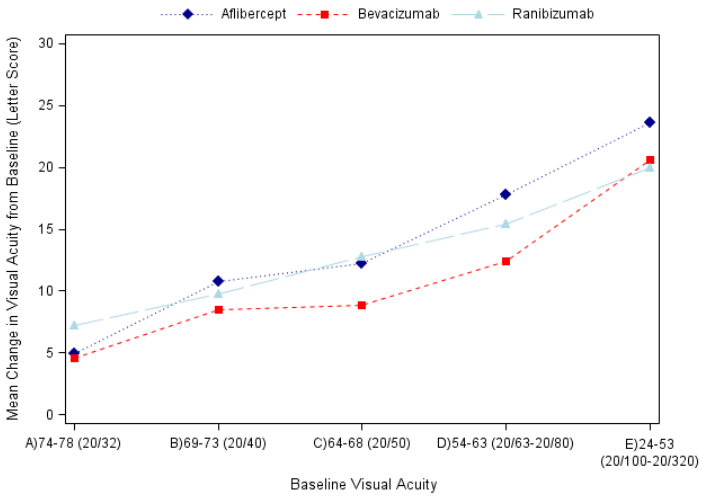


Figure S2B



Number of participants

Aflibercept	52	51	32	29	37
Bevacizumab	39	54	32	36	24
Ranibizumab	44	53	29	33	32

Change in visual acuity from baseline to 2 year, truncated to 3 standard deviations from the mean; stratified by baseline visual acuity (letter score and Snellen equivalent). **Panel A:** Box plots showing distribution of 2-year change in visual acuities; the horizontal line represents the median, the circle represents the mean, the ends of the box represent the 25th and 75th percentiles, the lines extending from each bar represent values up to 1.5*IQR, and the small circles represent outlier values beyond 1.5*IQR. **Panel B:** Mean change in visual acuity at 2 year.

Figure S3. Mean Change in Visual Acuity over Time in the Cohort of Participants Completing the 2 Year Visit, A) Overall; B) and C) Stratified by baseline visual acuity (approximate Snellen equivalent): 20/50 or worse (B) and 20/32-20/40 (C). Change in visual acuity was truncated to 3 standard deviations from the mean. The number of eyes at each time point ranged from 187-201 in the aflibercept group, 171-185 in the bevacizumab group, and 176-191 in the ranibizumab group

Figure S3A

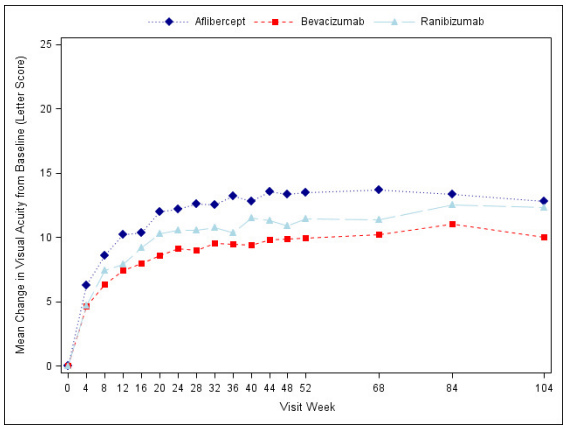


Figure S3B

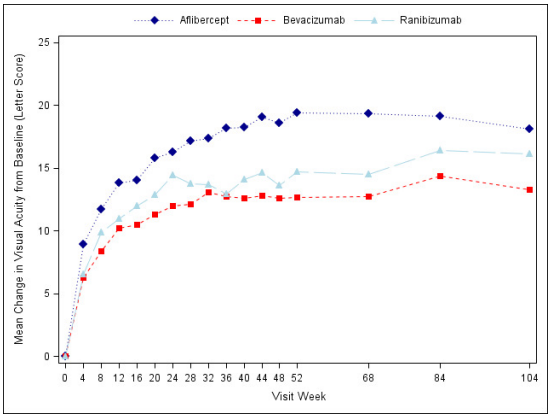


Figure S3C

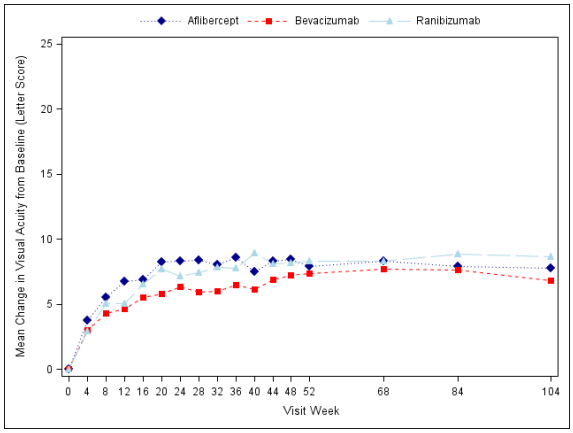


Figure S4. Proportion of Eyes with ≥10 Letter Improvement in Visual Acuity over Time, A) Overall; B) and C) Stratified by baseline visual acuity (approximate Snellen equivalent)**:** 20/50 or worse (B) and 20/32-20/40 (C). The number of eyes at each time point ranged from 195-224 in the aflibercept group, 185-218 in the bevacizumab group, and 188-218 in the ranibizumab group (see Figure S1 in the Supplementary Appendix and Figure S2 in the 1 Year Supplementary Appendix[1] for the number at each time point).

Figure S4A

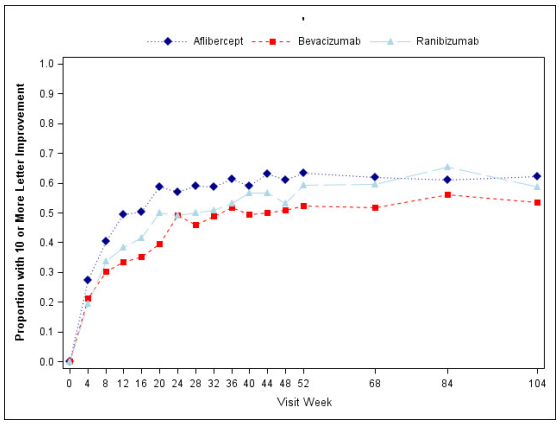


Figure S4B

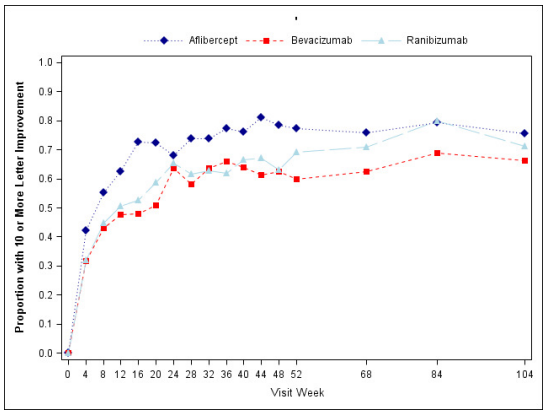


Figure S4C

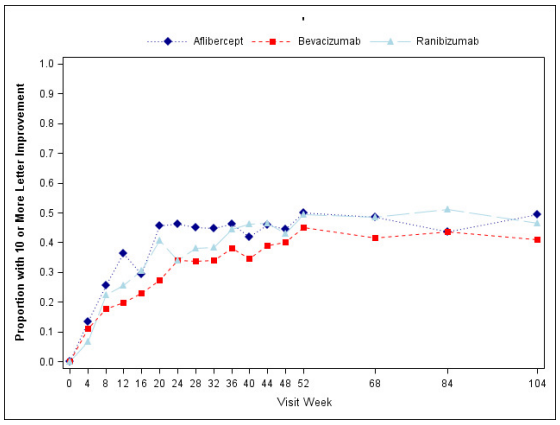


Figure S5. Mean change in VA over Time by Baseline Visual Acuity and Central Subfield Thickness. A. Worse VA and thicker. B. Worse VA and thinner C. Better VA and thicker. D. Better VA and thinner. Central subfield thickness values were translated to a Stratus equivalent thickness. The number of eyes at the 104 week time point for panels A, B, C, D, respectively, were: 58, 39, 31, 71 in the aflibercept group, 56, 34, 26, 67 in the bevacizumab group, and 46, 46, 38, 58 in the ranibizumab group

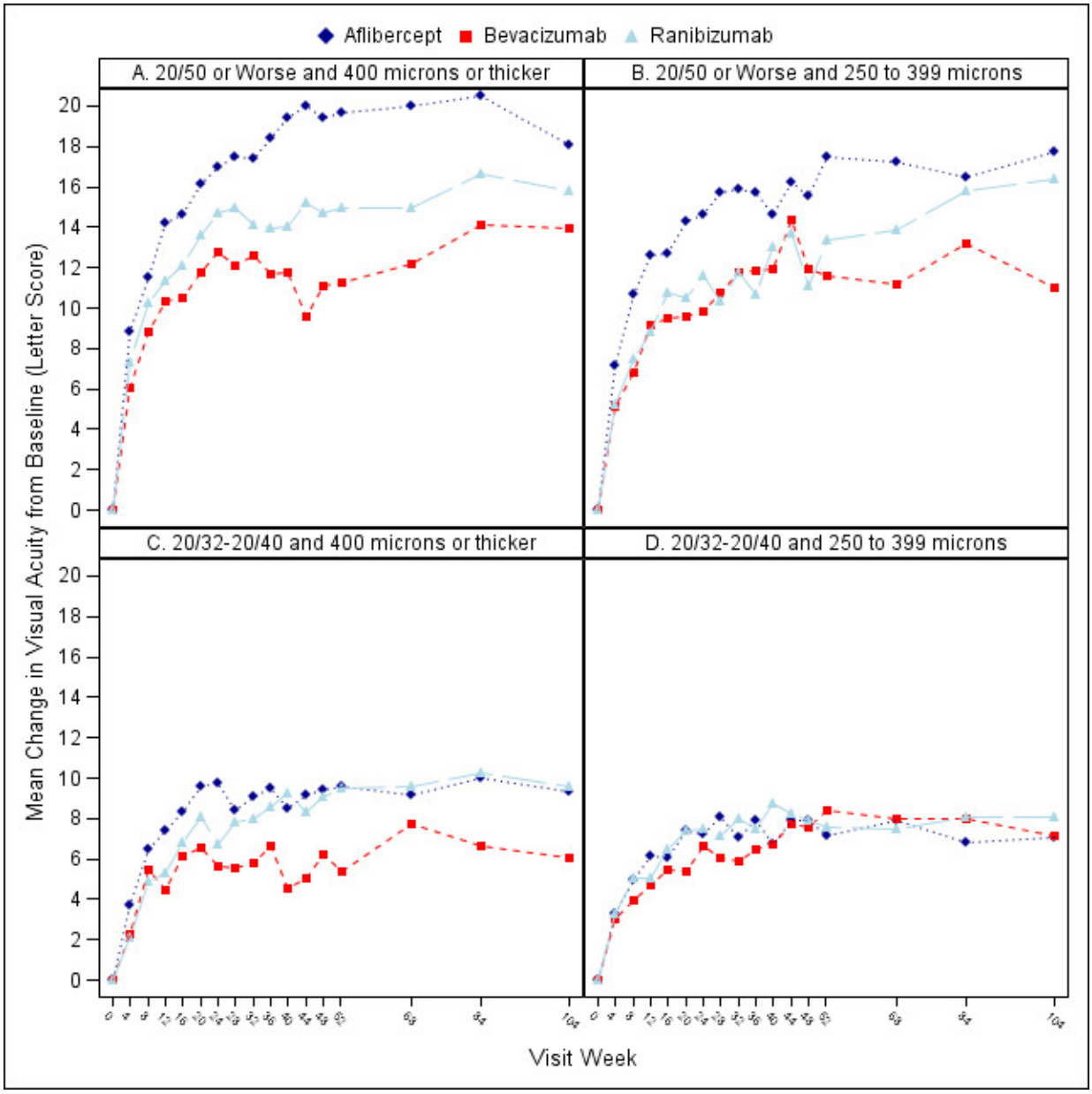


Figure S6. 2 Year Anti-Platelet Trialists' Collaboration (APTC) [5] Event Rates Across DME Studies of Anti-VEGF Agents

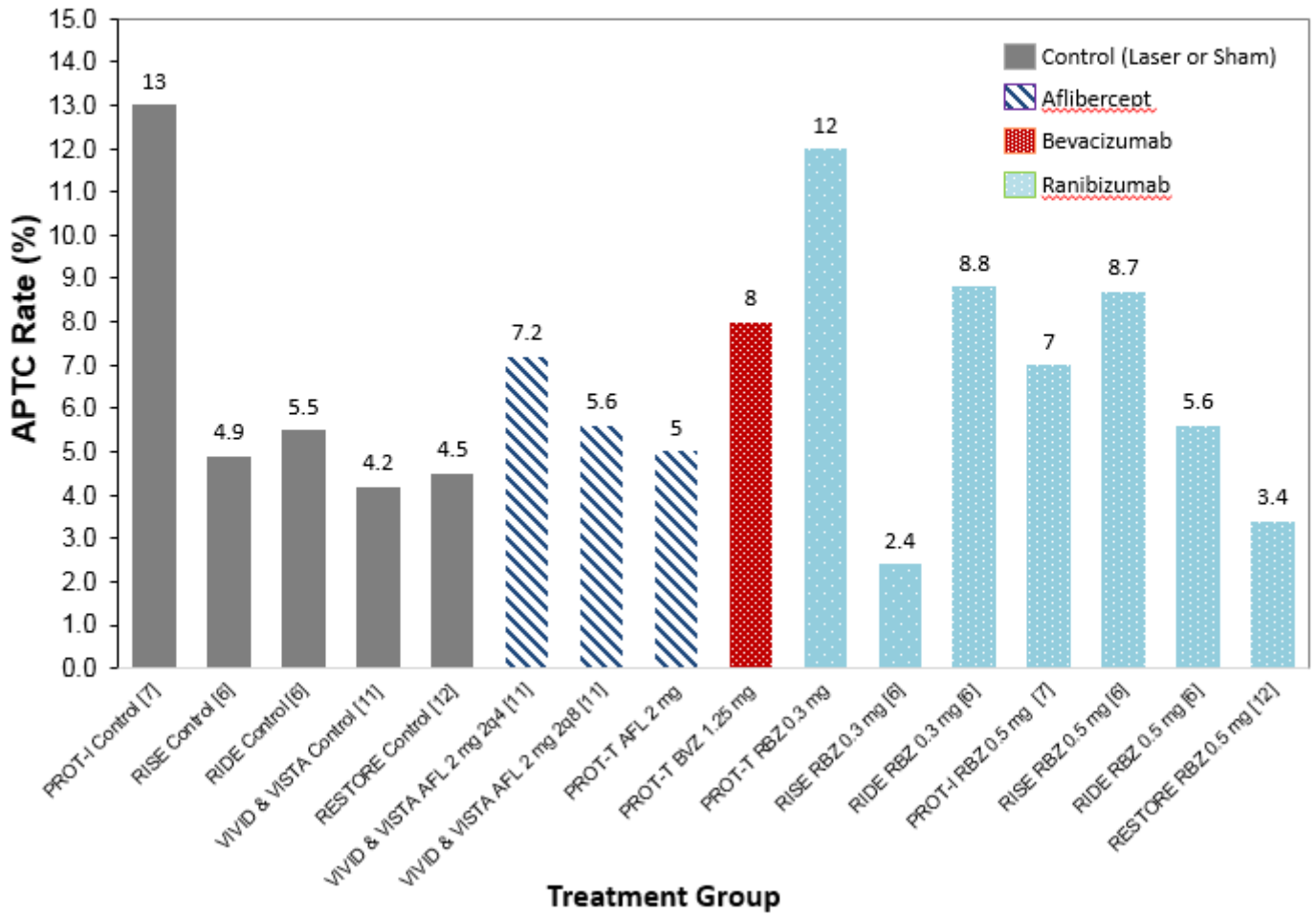


Table S1: Baseline Characteristics in Participants Completing vs. Not Completing the 2 Year Visit

	Completed 2 Year Visit			Did Not Complete 2 Year Visit (includes lost to follow up, withdrawn, death)		
	Aflibercept (N = 201)	**Bevacizumab (N = 185)**	**Ranibizumab (N = 192)**	**Aflibercept (N = 23)**	**Bevacizumab (N = 33)**	**Ranibizumab (N = 26)**
			Participant Characteristics			
Sex: Female - N (%)	93 (46%)	91 (49%)	85 (44%)	17 (74%)	12 (36%)	9 (35%)
Age (yrs) - Median (25th, 75th percentile)	61 (54, 66)	62 (56, 68)	59 (53, 67)	56 (52, 64)	64 (59, 72)	58 (52, 62)
Race/Ethnicity - N (%)						
White	133 (66%)	120 (65%)	129 (67%)	12 (52%)	19 (58%)	17 (65%)
Black/African-American	27 (13%)	31 (17%)	33 (17%)	5 (22%)	6 (18%)	3 (12%)
Hispanic	32 (16%)	30 (16%)	26 (14%)	5 (22%)	6 (18%)	4 (15%)
Asian	2 (<1%)	2 (1%)	2 (1%)	0	0	2 (8%)
Native Hawaiian/other Pacific Islander	1 (<1%)	1 (<1%)	0	1 (4%)	1 (3%)	0
American Indian/Alaskan Native	1 (<1%)	0	0	0	0	0
More than one race	4 (2%)	1 (<1%)	1 (<1%)	0	0	0
Unknown/not reported	1 (<1%)	0	1 (<1%)	0	1 (3%)	0
Diabetes Type - N (%)						
Type 1	21 (10%)	11 (6%)	15 (8%)	1 (4%)	1 (3%)	1 (4%)
Type 2	174 (87%)	173 (94%)	173 (90%)	22 (96%)	32 (97%)	23 (88%)
Uncertain	6 (3%)	1 (<1%)	4 (2%)	0	0	2 (8%)
Duration of Diabetes (yrs) - Median (25th, 75th percentile)	15 (8, 21)	17 (11, 25)	16 (12, 24)	15 (8, 21)	15 (10, 20)	17 (7, 21)
Hemoglobin A1c (%) - Median (25th, 75th percentile)*	7.6 (6.8, 9.0)	7.6 (6.7, 8.8)	8.0 (6.9, 9.3)	7.9 (6.8, 9.6)	8.0 (7.2, 8.8)	7.6 (6.6, 8.2)
			Ocular Characteristics			
Visual Acuity Letter Score - Median (75th, 25th percentile)	69 (59, 74)	69 (60, 73)	69 (60, 73)	68 (59, 73)	69 (59, 72)	65 (54, 71)
~ Snellen Equivalent - Median (75th, 25th percentile)	20/40 (20/63, 20/32)	20/40 (20/63, 20/40)	20/40 (20/63, 20/40)	20/50 (20/63, 20/40)	20/40 (20/63, 20/40)	20/50 (20/80, 20/40)
OCT Central Subfield (μm)† - Median (25th, 75th percentile)	385 (312, 462)	377 (308, 478)	387 (306, 477)	477 (283, 569)	370 (292, 467)	421 (345, 554)
OCT Retinal Volume (mm3)‡ - Median (25th, 75th percentile)	8.4 (7.7, 10.0)	8.4 (7.4, 9.8)	8.7 (7.7, 9.6)	9.8 (8.3, 10.9)	8.0 (7.4, 10.4)	9.5 (7.7, 10.4)

*Hemoglobin A1c missing for 5 in the completers aflibercept group, 1 in the non-completers ranibizumab group.

†central subfield thickness missing or not gradable in 2, 2, 3 completers and 1, 0, 0 non-completers in aflibercept, bevacizumab, and ranibizumab, respectively.

‡Volume missing or not gradable in 36, 31, 30 completers and 4, 4, 6 non-completers in aflibercept, bevacizumab, and ranibizumab, respectively.

Table S2. Visits and Treatment for Diabetic Macular Edema Overall

	Aflibercept	Bevacizumab	Ranibizumab	P-value
Visits				
Second Year – *2 year completers only*				
Number of Visits from 1 Year to 2 Year	**N=201**	**N=185**	**N=192**	
1	0	0	1 (1%)	
2	1 (1%)	0	0	
3	1 (1%)	4 (2%)	2 (1%)	
4	15 (7%)	16 (9%)	13 (7%)	
5	11 (5%)	8 (4%)	7 (4%)	
6	9 (4%)	8 (4%)	14 (7%)	
7	11 (5%)	17 (9%)	16 (8%)	
8	20 (10%)	15 (8%)	19 (10%)	
9	22 (11%)	19 (10%)	21 (11%)	
10	24 (12%)	12 (6%)	18 (9%)	
11	32 (16%)	32 (17%)	20 (10%)	
12	31 (15%)	34 (18%)	38 (20%)	
>=13	24 (12%)	20 (11%)	23 (12%)	
Mean (Standard Deviation)	9.4 (2.9)	9.3 (3.0)	9.3 (2.9)	
Median (25^{th}, 75^{th} percentile)	10 (8, 12)	10 (7, 12)	10 (7, 12)	
Injections				
Second Year – *2 year completers only*				
Number of Injections from 1 Year to 2 Year	**N=201**	**N=185**	**N=192****	
0	32 (16%)	30 (16%)	29 (15%)	
1	11 (5%)	11 (6%)	16 (8%)	
2	9 (4%)	14 (8%)	11 (6%)	
3	23 (11%)	8 (4%)	11 (6%)	
4	12 (6%)	13 (7%)	18 (9%)	
5	21 (10%)	16 (9%)	11 (6%)	
6	20 (10%)	12 (6%)	9 (5%)	
7	24 (12%)	14 (8%)	18 (9%)	
8	15 (7%)	18 (10%)	20 (10%)	
9	13 (6%)	18 (10%)	15 (8%)	
10	13 (6%)	13 (7%)	19 (10%)	
11	7 (3%)	9 (5%)	8 (4%)	
12	0	5 (3%)	6 (3%)	
>=13	1 (1%)	4 (2%)	1 (1%)	
Mean (Standard Deviation)	5.0 (3.4)	5.5 (3.9)	5.4 (3.8)	
Median (25^{th}, 75^{th} percentile)	5 (2, 7)	6 (2, 9)	6 (2, 9)	0.32*
Cumulative over 2 years– *2 year completers only*				
Number of Injections Prior to 2 Year	**N=201**	**N=185**	**N=192**,‡‡**	
Mean (Standard Deviation)	14.2 (4.6)	15.3 (5.3)	14.8 (5.0)	
Median (25^{th}, 75^{th} percentile)	15 (11, 17)	16 (12, 20)	15 (11, 19)	0.08*

	Aflibercept	Bevacizumab	Ranibizumab	P-value
All visits, prior to 2 year *– all available*				
Visits prior to 2 year where injection need was assessed	**N = 4561**	**N = 4382**	**N = 4399**	
Number of Visits with injections received	2998 (66%)	3115 (71%)	3066 (70%)	
Number of Visits with injections deferred due to				
success	141 (3%)	46 (1%)	127 (3%)	
stability	1303 (29%)	1134 (26%)	1121 (25%)	
failure	9 (<1%)	24 (1%)	3 (<1%)	
other reasons	110 (2%)	63 (1%)	82 (2%)	
Follow-up Visits Requiring Re-Injection Per Protocol based on OCT and visual acuity criteria	**N = 2844**	**N = 2915**	**N = 2901**	
Injection Not Given	74 (3%)	40 (1%)	60 (2%)	
Number of Injections Received when Protocol Indicated Deferral	1	17	5	
Laser				
Second Year*– 2 year completers only*				
	N=201	**N=185**	**N=192**	
Total Number of Laser Treatments between 1 Year and 2 Years				
0	160 (80%)	127 (69%)	140 (73%)	0.046†
1	31 (15%)	42 (23%)	27 (14%)	
2	8 (4%)	12 (6%)	17 (9%)	
3	2 (1%)	4 (2%)	8 (4%)	
Mean (Standard Deviation)	0.3 (0.6)	0.4 (0.7)	0.4 (0.8)	
Median (25^{th}, 75^{th} percentile)	0 (0,0)	0 (0,1)	0 (0,1)	
Cumulative during 2 years*– 2 year completers only*				
	N=201	**N=185**	**N=192**	
Total Number of Laser Treatments Between 24 weeks and 2 Years				
0	118 (59%)	66 (36%)	93 (48%)	<0.001‡
1	46 (23%)	60 (32%)	48 (25%)	
2	21 (10%)	35 (19%)	26 (14%)	
3	10 (5%)	18 (10%)	15 (8%)	
4-5	6 (3%)	6 (3%)	10 (5%)	
Mean (Standard Deviation)	0.7 (1.1)	1.1 (1.1)	1.0 (1.2)	
Median (25^{th}, 75^{th} percentile)	0 (0,1)	1 (0, 2)	1 (0,2)	
Non-Protocol Treatments for DME				
Cumulative over 2 years*– all randomized eyes*				
	N=224	N=218	N=218	
Eyes receiving 1 or more alternative treatments for DME other than laser – N (%)	3 (1%) / (1)	10 (5%) / (6)	1 (<1%) / (0)	

	Aflibercept	Bevacizumab	Ranibizumab	P-value
/ (Number of those eyes meeting failure criteria)				
Alternative treatment(s) received				
Aflibercept	0	2	0	
Aflibercept/Corticosteroid	0	1	0	
Aflibercept/Ranibizumab	0	1	0	
Aflibercept/Corticosteroid/Ranibizumab	0	1	0	
Corticosteroid/Ranibizumab	0	1	0	
Bevacizumab	0	0	1	
Ranibizumab	1	3	0	
Corticosteroid	2	1	0	

DME = Diabetic macular edema

* Global (overall 3 group comparison) P-value from Kruskal-Wallis Test for number of injections in the given time interval.

†Global (overall 3 group comparison) P-value from Fisher's Test for proportion with no laser versus any laser in the given time interval. Pairwise comparisons from Fisher's Exact Test (adjusted for multiple comparisons by taking the maximum of the global and pairwise comparison P-values): aflibercept-bevacizumab: P=0.046, aflibercept-ranibizumab: P=0.12, bevacizumab-ranibizumab: P=0.37.

‡Global (overall 3 group comparison) P-value from Fisher's Test for proportion with no laser versus any laser in the given time interval. Pairwise comparisons from Fisher's Exact Test (adjusted for multiple comparisons by taking the maximum of the global and pairwise comparison P-values): aflibercept-bevacizumab: P=<0.001, aflibercept-ranibizumab: P=0.04, bevacizumab-ranibizumab: P=0.01.

**1 ranibizumab eye had 3 injections of commercial ranibizumab (not through the study). These injections are not counted in the injection counts, and 2 of these are counted as injections required but not given via the protocol system.

‡‡Seven ranibizumab eyes received 1 injection and 2 ranibizumab eyes received 2 injections of 0.5 mg of ranibizumab prior to the FDA approving a 0.3mg dosage of ranibizumab for DME treatment.

Success: before the 24-week visit, visual acuity letter score was ≥84 (20/20 or better) with CST <250 microns Stratus equivalent and no "improvement" (at least a 5 letter gain or at least a 10% reduction in CST) from the last two injections.
Stability: starting at the 24-week visit, no "improvement" and no "worsening" (at least a 5-letter change or 10% change in CST) after two consecutive injections
Failure: starting at the 24-week visit, OCT CST >= 250 microns Stratus equivalent, visual acuity 10 or more letters worse than baseline at 2 consecutive visits, DME present on clinical exam that the investigator believes is the cause of the visual loss, complete laser has been given , not "improved" (OCT CST decreased by <10% [or increased] AND visual acuity letter score improved by <5 letters) since either of the last two injections, not "improved" (OCT CST decreased by <10% [or increased] AND visual acuity letter score improved by <5 letters) since the last laser treatment was given, AND >= 13 weeks since the last laser treatment.

Table S3. Visual Acuity at 2 Years – Overall

	Observed Data			Treatment Group Comparisons Differences in Mean Change or Difference in Proportions Adjusted 95% CI and Adjusted P Value		
	Aflibercept (N = 201)	**Bevacizumab (N = 185)**	**Ranibizumab (N = 191)**	**Aflibercept vs Bevacizumab**	**Aflibercept vs Ranibizumab**	**Ranibizumab vs Bevacizumab**
Baseline						
Mean ± SD	64.9 ± 11.9	65.0 ± 11.1	64.9 ± 11.4			
~ Snellen equivalent	20/50	20/50	20/50			
1 Year (in 2 year cohort*)						
Mean ± SD	78.4 ± 9.8	74.7 ± 12.4	76.4 ± 11.2			
~ Snellen equivalent	20/32	20/32	20/32			
Mean Change ±SD	13.5 ± 11.1	10.0 ± 10.1	11.5 ± 9.2			
2 Year						
Mean ± SD	77.8 ± 11.5	74.6 ± 14.5	77.1 ± 12.4			
~ Snellen equivalent	20/32	20/32	20/32			
Change from baseline (letter score)						
Mean ± SD	+12.8 ± 12.4	+10.0 ± 11.8	+12.3 ± 10.5	+2.7 (+0.3 to +5.2) P=0.02	+0.7 (-1.3 to +2.8) P=0.47	+2.0 (-0.4 to +4.4) P=0.11
≥ 10 letter improvement	125 (62%)	99 (54%)	112 (59%)	+9% (-3% to +20%) P=0.22	+3% (-6% to +12%) P=0.51	+6% (-5% to +17%) P=0.50
≥ 10 letters worsening	9 (4%)	12 (6%)	3 (2%)	-1% (-6% to +3%) P=0.49	+2% (-2% to +6%) P=0.39	-4% (-8% to +1%) P=0.15
≥ 15 letter improvement	78 (39%)	64 (35%)	70 (37%)	+4% (-5% to +13%) P=0.70	+2% (-7% to +10%) P=0.70	+2% (-6% to +11%) P=0.70
≥ 15 letters worsening	5 (2%)	6 (3%)	3 (2%)	0% (-3% to +3%) P=0.84	+1% (-2% to +4%) P=0.84	-1% (-4% to +2%) P=0.84

SD = Standard deviation, CI = Confidence interval

Treatment group comparisons are from ANCOVA models adjusted for continuous baseline visual acuity or from binomial regression models adjusted for categorical baseline visual acuity. Reported P-values have been adjusted for multiple treatment group comparisons to account for an overall Type 1 error rate of 0.049 (see Hochberg for computation of the Hochberg-adjusted P-values[2]) and corresponding (1-α/i)*100% confidence intervals were reported, where i is the rank (1, 2, or 3) of the Hochberg-adjusted P-value from among the descending ordered raw pairwise P-values. This could result in identical P-values for all three pairwise comparisons.

Tests for treatment group interaction with baseline visual acuity from ANCOVA model for mean change in visual acuity adjusted for baseline visual acuity (using the multiple imputation datasets and computing the P-value associated with the average of the F statistics from each imputed dataset):

- **P-value for interaction, treating baseline visual acuity as continuous = 0.02**
- **P-value for interaction, treating baseline visual acuity as categorical (<69 versus ≥69) = 0.11**

Visual acuity change truncated using 1 year mean +/- 3SD (-22 and +44) to minimize the effects of outliers for 6 eyes in the aflibercept group (3 on the positive end, 3 on the negative end) , 5 eyes in the bevacizumab group (1 on the positive end , 4 on the negative end), and 4 eyes in the ranibizumab group (1 on the positive end , 3 on the negative end).

2-year visit data unavailable for 23 eyes in the aflibercept group, 33 eyes in the bevacizumab group, and 27 eyes (including one eye which had a 2 year visit but was missing visual acuity at the visit) in the ranibizumab group. Descriptive statistics were based on observed data; Markov chain Monte Carlo multiple imputation[3] (100 imputations) was used to estimate the missing 2 year change in visual acuity for the treatment group comparisons (including tests for interaction).

*One eye in the aflibercept group in the 2 year cohort was missing 1 year.

Table S4. Visual Acuity at 2 Year: Sensitivity Analysis				
Primary analyses are indicated in bold	**Mean Change in Visual Acuity at 2 Years ± SD**			**Hochberg-adjusted[2] P-values for AvB, AvR, BvR**
	Aflibercept	**Bevacizumab**	**Ranibizumab**	
Overall	**Ns Observed=201 Imputation=224**	**Ns Observed=185 Imputation=218**	**Ns Observed=191 Imputation=218**	
Observed data only, VA Change Not Truncated	+12.9 ±13.2	+9.6 ± 13.9	+12.2 ± 11.2	0.02, 0.51, 0.07
Observed data only	**+12.8 ± 12.4**	**+10.0 ± 11.8**	**+12.3 ± 10.5**	0.03, 0.62, 0.07
LOCF Imputation, VA Change Not Truncated	+12.3 ± 13.0	+9.2 ± 13.3	+11.3 ± 11.8	0.02, 0.29, 0.17
LOCF Imputation	+12.2 ± 12.3	+9.6 ±11.4	+11.5 ± 11.1	0.03, 0.38, 0.17
Multiple Imputation, VA Change Not Truncated	+12.6 ± 13.5	+9.3 ± 14.2	+11.8 ± 12.1	0.01, 0.37, 0.11
Multiple Imputation	+12.5 ± 12.7	+9.8 ± 12.0	+12.0 ± 11.2	**0.02, 0.47, 0.11**
Multiple Imputation, adjusting for potential confounders*				0.06, 0.53, 0.17
Observed data only; converting visual acuity change scores to normalized ranks (van der Waerden scores)				0.02, 0.56, 0.06
Observed data only; Wilcoxon rank sum test				0.15, 0.60, 0.23
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME [†]				0.17, 0.51, 0.43
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME or for which an injection deviation occurred[‡]				0.07, 0.78, 0.09
Baseline Visual Acuity 20/50 or Worse (Letter Score <69)	**Ns Observed=98 Imputation=112**	**Ns Observed=92 Imputation=107**	**Ns Observed=94 Imputation=110**	
Observed data only, VA Change Not Truncated	+18.5 ± 14.7	+12.9 ± 15.4	+15.8 ± 13.3	0.03, 0.20, 0.20
Observed data only	**+18.1 ± 13.8**	**+13.3 ± 13.4**	**+16.1 ± 12.1**	0.048, 0.29, 0.29
LOCF Imputation, VA Change Not Truncated	+17.2 ± 14.7	+12.0 ± 15.0	+14.3 ± 14.5	0.02, 0.18, 0.32
LOCF Imputation	+16.9 ± 13.9	+12.4 ± +13.2	+14.7 ± +13.1	0.03, 0.26, 0.26
Multiple Imputation, VA Change Not Truncated	+17.7 ± 14.9	+12.2 ± 15.5	+15.1 ±14.2	0.01, 0.20, 0.20
Multiple Imputation	+17.5 ± 14.0	+12.7 ±13.6	+15.4 ± 12.9	**0.02, 0.18, 0.18**

Multiple Imputation, adjusting for potential confounders*				0.08, 0.33, 0.33
Observed data only; converting visual acuity change scores to normalized ranks (van der Waerden scores)				0.06, 0.27, 0.27
Observed data only; Wilcoxon rank sum test				0.07, 0.24, 0.24
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME †				0.29, 0.47, 0.61
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME or for which an injection deviation occurred‡				0.12, 0.55, 0.30
Baseline Visual Acuity 20/32-20/40 (Letter Score >= 69)	**Ns Observed=103 Imputation=112**	**Ns Observed=93 Imputation=111**	**Ns Observed=97 Imputation=108**	
Observed data only, VA Change Not Truncated	+7.7 ± 8.9	+6.3 ± 11.5	+8.6 ± 7.0	0.32, 0.49, 0.12
Observed data only	**+7.8 ± 8.4**	**+6.8 ± 8.8**	**+8.6 ± 7.0**	0.36, 0.49, 0.14
LOCF Imputation, VA Change Not Truncated	+7.3 ± 8.8	+6.5 ± 10.9	+8.3 ± 7.3	0.47, 0.50, 0.19
LOCF Imputation	+7.5 ±8.3	+6.9 ± 8.6	+8.3 ± 7.3	0.51, 0.51, 0.24
Multiple Imputation, VA Change Not Truncated	+7.4 ± 9.5	+6.5 ± 12.0	+8.4 ± 8.2	0.52, 0.52, 0.26
Multiple Imputation	+7.6 ± 8.8	+7.1 ± 9.6	+8.4 ± 7.8	**0.51, 0.51, 0.31**
Multiple Imputation, adjusting for potential confounders*				0.48, 0.68, 0.38
Observed data only; converting visual acuity change scores to normalized ranks (van der Waerden scores)				0.32, 0.56, 0.15
Observed data only; Wilcoxon rank sum test				0.60, 0.73, 0.42
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME †				0.45, 0.59, 0.25
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME or for which an injection deviation occurred‡				0.45, 0.74, 0.36

VA change truncated unless otherwise stated. Treatment group comparisons of mean change are from ANCOVA models adjusting for continuous baseline visual acuity unless otherwise stated. VA = Visual acuity; LOCF=Last observation carried forward; DME = Diabetic macular edema.

*Any prior DME treatment, age, baseline central subfield thickness, diabetes type, baseline lens status, and baseline Hemoglobin A1c

†Overall: 2 in the aflibercept group, 9 in the bevacizumab group, and 0 in the ranibizumab group.

‡ Overall: 42 in the aflibercept group, 35 in the bevacizumab group, and 33 in the ranibizumab group.

Multiple imputation = Markov chain Monte Carlo multiple imputation[3] (100 imputations) was used to estimate the missing 2 year change in visual acuity for the treatment group comparisons

Table S5. Detailed Distribution of Visual Acuity at 2 Years According to Baseline Visual Acuity Subgroup

Baseline Visual Acuity 20/50 or Worse (Letter Score <69)

	Aflibercept (N = 98)	Bevacizumab (N = 92)	Ranibizumab (N = 94)
~Snellen Equivalent (Letter Score)			
20/12.5 (94-98)	0	0	2(2%)
20/16 (89-93)	7 (7%)	2 (2%)	6 (6%)
20/20 (84-88)	16 (16%)	9 (10%)	12 (13%)
20/25 (79-83)	21 (21%)	19 (21%)	9 (10%)
20/32 (74-78)	16 (16%)	13 (14%)	22 (23%)
20/40 (69-73)	15 (15%)	20 (22%)	12 (13%)
20/50 (64-68)	10 (10%)	8 (9%)	9 (10%)
20/63 (59-63)	4 (4%)	5 (5%)	7 (7%)
20/80 (54-58)	2 (2%)	5 (5%)	6 (6%)
20/100 (49-53)	1 (1%)	2 (2%)	6 (6%)
20/125 (44-48)	2 (2%)	3 (3%)	1 (1%)
20/160 (39-43)	1 (1%)	1 (1%)	0
20/200 (34-38)	0	3 (3%)	0
20/250 (29-33)	1 (1%)	0	0
20/320 (24-28)	2 (2%)	0	1 (1%)
20/400 (19-23)	0	0	0
<20/400 (<19)	0	2 (2%)	1 (1%)

Baseline Visual Acuity 20/32-20/40 (Letter Score 78- 69)

	Aflibercept (N = 103)	Bevacizumab (N = 93)	Ranibizumab (N = 97)
~Snellen Equivalent (Letter Score)			
20/12.5 (94-98)	1 (1%)	3 (3%)	2 (2%)
20/16 (89-93)	14 (14%)	11 (12%)	12 (12%)
20/20 (84-88)	33 (32%)	16 (17%)	29 (30%)
20/25 (79-83)	25 (24%)	23 (25%)	29 (30%)
20/32 (74-78)	12 (12%)	25 (27%)	15 (15%)
20/40 (69-73)	12 (12%)	9 (10%)	7 (7%)
20/50 (64-68)	1 (1%)	2 (2%)	2 (2%)
20/63 (59-63)	4 (4%)	2 (2%)	0
20/80 (54-58)	0	0	0
20/100 (49-53)	0	1 (1%)	1 (1%)
20/125 (44-48)	0	0	0
20/160 (39-43)	0	0	0
20/200 (34-38)	1 (1%)	0	0
20/250 (29-33)	0	0	0
20/320 (24-28)	0	0	0
20/400 (19-23)	0	0	0
<20/400 (<19)	0	1 (1%)	0

Table S6 Change in Visual Acuity Letter Score from Baseline to 2 Year: Additional Pre-Planned Subgroup Analyses							
	Aflibercept		Bevacizumab		Ranibizumab		P Value for Interaction Categorical (Continuous)
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
Baseline OCT Central Subfield Thickness							0.68 (0.23)
< 400 µm	110	10.9±11.3	101	8.4±10.2	104	11.8±10.5	
≥ 400 µm	89	15.0±13.3	82	11.5±12.9	84	13.0±10.5	
Any Prior Anti-VEGF Treatment							0.45
No	179	13.0±12.9	153	10.6±11.4	167	12.7±10.6	
Yes	22	11.4±8.3	32	7.6±13.1	24	9.7±9.2	
Lens Status							0.69
Pseudophakic	51	12.8±11.1	49	8.2±11.7	40	11.5±8.2	
Phakic	150	12.9±12.9	136	10.7±11.8	151	12.5±11.0	

SD = standard deviation, OCT= optical coherence tomography, VEGF= vascular endothelial growth factor

Visual acuity change truncated to +/- 3SD.

An additional preplanned hypothesis to look at prior vitrectomy subgroups did not have at least 10 eyes in each treatment group for each subgroup and was therefore not evaluated.

Descriptive statistics were based on observed data; Markov chain Monte Carlo multiple imputation[3] (100 imputations) was used to estimate the missing 2 year change in visual acuity for the tests for interaction. Tests for treatment group interaction were from ANCOVA model for mean change in visual acuity adjusted for continuous baseline visual acuity (using the multiple imputation datasets and computing the *P*-value associated with the average of the F statistics from each imputed dataset).

Table S7. Optical Coherence Tomography Central Subfield Thickness Outcomes Overall

	Observed Data			Treatment Group Comparisons Differences in Mean Change or Difference in Proportions Adjusted 95% CI and Adjusted P Value		
	Aflibercept (N = 198)	**Bevacizumab (N = 182)**	**Ranibizumab (N = 186)**	**Aflibercept vs Bevacizumab**	**Aflibercept vs Ranibizumab**	**Ranibizumab vs Bevacizumab**
Baseline CSF Mean ± SD	411 ± 131	415 ± 134	403 ± 120			
1 year (in 2 year cohort*)						
Mean ± SD	239± 66	310 ±121	254 ±89			
Mean change ± SD	-169 ± 139	-102 ± 124	-147 ± 134			
2 year						
Mean ± SD	237± 68	286 ±102	251 ±99			
Mean change ± SD	-171 ± 141	-126 ± 143	-149 ± 141	-48.5 (-70.0,-27.0) P<0.001	-15.5 (-33.0,+2.0) P=0.08	-33.0 (-53.4,-12.6) P<0.001
CSF <250 µm	141 (71%)	75 (41%)	121 (65%)	+32% (+20%, +43%) P<0.001	+6% (-3%, +16%) P=0.20	+25% (+14%, +37%) P<0.001

CSF = central subfield, CI = confidence interval, SD = standard deviation

In addition to participants missing the 2-year visit (see Figure S1), 3 in the aflibercept group, 3 in the bevacizumab group, and 6 in the ranibizumab group had 2-year visits but unusable OCT data to compute change due to the scan being missing or ungradable at either baseline or 2 year.

Baseline CSF values were converted from the thickness value measured on a Spectralis or Cirrus OCT machine to a Stratus equivalent value for 540 scans. 2-year CSF values were converted from a thickness value measured on a Spectralis or Cirrus OCT machine to a Stratus equivalent value for 563 scans. When calculating change in CSF thickness, measurements taken on the same machine at both visits were not converted, since the conversion equation slope is nearly 1 and the constant difference does not affect the change calculation. Therefore, change in CSF thickness was calculated after converting either the baseline and/or follow-up thickness value from Spectralis or Cirrus to a Stratus equivalent value in 34 eyes.

Treatment group comparison results are from ANCOVA on observed data, adjusted for continuous baseline visual acuity and continuous baseline CSF or from Poisson regression models with robust variance estimation using identity link[4], adjusted for categorical baseline visual acuity and categorical baseline CSF. Reported P-values have been adjusted for multiple treatment group comparisons to account for an overall Type 1 error rate of 0.049 (see Hochberg for computation of the Hochberg-adjusted P-values[2]) and corresponding (1-α/i)*100% confidence intervals were reported, where i is the rank (1, 2, or 3) of the Hochberg-adjusted P-value from among the descending ordered raw pairwise P-values. This could result in identical P-values for all three pairwise comparisons.

Tests for treatment group interaction with baseline visual acuity from ANCOVA model for mean change in CSF adjusted for baseline visual acuity and continuous baseline CSF:

- **P-value for interaction, treating baseline visual acuity as continuous <0.001.**
- **P-value for interaction, treating baseline visual acuity as categorical (<69 versus ≥69) <0.001.**

*2 in the aflibercept group, 1 in the bevacizumab group, and 2 in the ranibizumab group were in the 2 year cohort but missing 1 year.

Table S8. Change in Retinal Volume from Baseline to 2 Year

Overall

	Aflibercept (N = 163)	Bevacizumab (N = 153)	Ranibizumab (N = 159)
Baseline Volume - Mean ± SD	8.9±1.8	8.9±2.0	9.0±1.8
Volume at 2 Year - Mean ± SD	7.2±0.9	7.5±1.1	7.3±1.2
Change in Volume from Baseline - Mean ± SD	-1.8±1.7	-1.4±1.8	-1.7±1.7

Baseline Visual Acuity 20/50 or Worse (Letter Score <69)

	Aflibercept (N = 78)	Bevacizumab (N = 71)	Ranibizumab (N = 73)
Baseline Volume - Mean ± SD	9.6±2.1	9.6±2.4	9.4±2.2
Volume at 2 Year - Mean ± SD	7.2±1.1	7.5±1.0	7.3±1.5
Change in Volume from Baseline - Mean ± SD	-2.3±1.8	-2.1±2.0	-2.1±2.0

Baseline Visual Acuity 20/32-20/40 (Letter Score 78-69)

	Aflibercept (N = 85)	Bevacizumab (N = 82)	Ranibizumab (N = 86)
Baseline Volume - Mean ± SD	8.3±1.2	8.2±1.3	8.6±1.4
Volume at 2 Year - Mean ± SD	7.1±0.8	7.5±1.1	7.2±0.9
Change in Volume from Baseline - Mean ± SD	-1.2±1.3	-0.7±1.1	-1.3±1.3

SD = standard deviation

In addition to participants missing the 2-year visit (see Figure S1), 38 in the aflibercept group, 32 in the bevacizumab group, and 33 in the ranibizumab group had 2-year visits but unusable OCT data to compute change due to the scan being missing or ungradable at either baseline or 2 year.

Baseline volume values were converted from the thickness value measured on a Spectralis or Cirrus OCT machine to a Stratus equivalent value for 456 scans. 2-year volume values were converted from a thickness value measured on a Spectralis or Cirrus OCT machine to a Stratus equivalent value for 472 scans. When calculating change in volume, measurements taken on the same machine at both visits were not converted, because the conversion equation slope is nearly 1 and the constant difference does not affect the change calculation. Therefore, change in volume was calculated after converting either the baseline and/or follow-up value from Spectralis or Cirrus to a Stratus equivalent value in 26 eyes.

Table S9. Pre-Specified Systemic Adverse Events through 2 Year: Stratified by Whether Bilateral Study Drug was Received at any Time During the Study			
Participants with Unilateral Study Anti-VEGF Treatment at all times during the study			
	Aflibercept (N = 80)	**Bevacizumab (N = 84)**	**Ranibizumab (N = 86)**
Vascular Events According to the Antiplatelet Trialists' Collaboration[5] occurring at least once at any time during the study (No. Participants)			
Non-fatal myocardial infarction	2 (3%)	0	2 (2%)
Non-fatal stroke	1 (1%)	3 (4%)	4 (5%)
Vascular death (from any potential vascular or unknown cause)	1 (1%)	4 (5%)	4 (5%)
Any Antiplatlet Trialists` Collaboration Event	4 (5%)	7 (8%)	10 (12%)
Pre-specified Systemic Events occurring at least once at any time during the study (No. Participants)			
Death (any cause)	2 (3%)	7 (8%)	6 (7%)
Hospitalization	28 (35%)	23 (27%)	29 (34%)
Serious adverse event	34 (43%)	27 (32%)	32 (37%)
Gastrointestinal‡	22 (28%)	22 (26%)	24 (28%)
Kidney§	16 (20%)	9 (11%)	6 (7%)
Hypertension	10 (13%)	6 (7%)	10 (12%)
Participants with Bilateral Study Anti-VEGF Treatment at any time during the study			
	Aflibercept (N = 144)	**Bevacizumab (N = 134)**	**Ranibizumab (N = 132)**
Vascular Events According to the Antiplatelet Trialists' Collaboration[5] occurring at least once at any time during the study (No. Participants)			
Non-fatal myocardial infarction	5 (3%)	3 (2%)	4 (3%)
Non-fatal stroke	1 (<1%)	3 (2%)	7 (5%)
Vascular death (from any potential vascular or unknown cause)	2 (1%)	4 (3%)	5 (4%)
Any Antiplatlet Trialists` Collaboration Event	8 (6%)	10(7%)	16 (12%)
Pre-specified Systemic Events occurring at least once at any time during the study (No. Participants)			
Death (any cause)	3 (2%)	6 (4%)	5 (4%)
Hospitalization	49 (34%)	48 (36%)	44 (33%)
Serious adverse event	54 (38%)	54 (40%)	50 (38%)
Gastrointestinal‡	45 (31%)	42 (31%)	36 (37%)
Kidney§	34 (24%)	37 (28%)	29 (22%)
Hypertension	29 (20%)	21 (16%)	34 (26%)

‡Includes events with a Medical Dictionary for Regulatory Activities system organ class of gastrointestinal disorder.

§Includes a subset of Medical Dictionary for Regulatory Activities system organ class of renal and urinary disorders events indicative of intrinsic kidney disease, plus increased/abnormal blood creatinine or renal transplant from other system organ classes.

Table S10. Post Hoc Analysis: Antiplatlet Trialists` Collaboration Events through 2 Year: Stratified by Whether Participant had Myocardial Infarction or Stroke Prior to Baseline			
Participants with No Myocardial Infarction or Stroke Prior to Baseline			
	Aflibercept (N = 203)	**Bevacizumab (N = 193)**	**Ranibizumab (N = 193)**
Vascular Events According to the Antiplatelet Trialists' Collaboration[5] occurring at least once at any time during the study (No. Participants)			
Non-fatal myocardial infarction	6 (3%)	3 (2%)	4 (2%)
Non-fatal stroke	2 (<1%)	5 (3%)	6 (3%)
Vascular death (from any potential vascular or unknown cause)	2 (<1%)	4 (2%)	7 (4%)
Any Antiplatlet Trialists` Collaboration Event	10 (5%)	12 (6%)	17 (9%)
Participants with Myocardial Infarction or Stroke Prior to Baseline			
	Aflibercept (N = 21)	**Bevacizumab (N = 25)**	**Ranibizumab (N = 25)**
Vascular Events According to the Antiplatelet Trialists' Collaboration[5] occurring at least once at any time during the study (No. Participants)			
Non-fatal myocardial infarction	1 (5%)	0	2 (8%)
Non-fatal stroke	0	1 (4%)	5 (20%)
Vascular death (from any potential vascular or unknown cause)	1 (5%)	4 (16%)	2 (8%)
Any Antiplatlet Trialists` Collaboration Event	2 (10%)	5 (20%)	9 (36%)

Global P-value from Poisson model with robust variance estimation using the log link[4] adjusting for prior myocardial infarction, prior stroke: P=0.06.

Table S11. Post Hoc Analysis: Events by Medical Dictionary for Regulatory Activities System Organ Class at any Time During the Study

	Aflibercept (N = 224)	Bevacizumab (N = 218)	Ranibizumab (N = 218)	P Value*
Number of Participants with an Event in the Given System Organ Class				
Blood and lymphatic system disorders	27 (12%)	22 (10%)	19 (9%)	0.52
Cardiac disorders	28 (13%)	28 (13%)	40 (18%)	0.16
Ear and labyrinth disorders	11 (5%)	8 (4%)	2 (1%)	0.04**
Endocrine disorders	44 (20%)	43 (20%)	39 (18%)	0.86
Eye disorders	191 (85%)	192 (88%)	187 (86%)	0.66
Gastrointestinal disorders	67 (30%)	64 (29%)	60 (28%)	0.85
General disorders and administration site conditions	51 (23%)	49 (22%)	39 (18%)	0.38
Hepatobiliary disorders	4 (2%)	7 (3%)	3 (1%)	0.44
Immune system disorders	19 (8%)	17 (8%)	14 (6%)	0.70
Infections and infestations	40 (18%)	49 (22%)	41 (19%)	0.44
Injury, poisoning and procedural complications	31 (14%)	32 (15%)	25 (11%)	0.58
Investigations	35 (16%)	28 (13%)	36 (17%)	0.53
Metabolism and nutrition disorders	49 (22%)	39 (18%)	39 (18%)	0.49
Musculoskeletal and connective tissue disorders	76 (34%)	81 (37%)	76 (35%)	0.76
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (2%)	6 (3%)	5 (2%)	0.95
Nervous system disorders	61 (27%)	59 (27%)	73 (33%)	0.25
Psychiatric disorders	22 (10%)	25 (11%)	23 (11%)	0.88
Renal and urinary disorders	66 (29%)	63 (29%)	51 (23%)	0.29
Reproductive system and breast disorders	7 (3%)	6 (3%)	9 (4%)	0.74
Respiratory, thoracic and mediastinal disorders	101 (45%)	98 (45%)	96 (44%)	0.98
Skin and subcutaneous tissue disorders	54 (24%)	43 (20%)	46 (21%)	0.52
Social circumstances	0	1 (<1%)	0	0.66
Surgical and medical procedures	24 (11%)	27 (12%)	29 (13%)	0.72
Vascular disorders	53 (24%)	47 (22%)	67 (31%)	0.07

*Global (overall 3 group comparison) P-value from Fisher's Exact Test.

**Pairwise comparisons from Fisher's Exact Test (adjusted for multiple comparisons by taking the maximum of the global and pairwise comparison P-values): aflibercept-bevacizumab: P=0.64, aflibercept-ranibizumab: P=0.04, bevacizumab-ranibizumab: P=0.11.

Table S12. Post Hoc Analysis: Cardiovascular Events at any Time During the Study				
Overall				
Events occurring at least once (No. Participants)	**Aflibercept (N = 224)**	**Bevacizumab (N = 218)**	**Ranibizumab (N = 218)**	**P Value**
Any Cardiovascular Event,† excluding Hypertension	44 (20%)	49 (22%)	59 (27%)	0.18*
Any Cardiovascular Event†	69 (31%)	69 (32%)	82 (38%)	0.26‡
Cardiac Events	30 (13%)	34 (16%)	41 (19%)	
Cerebrovascular Events	4 (2%)	8 (4%)	18 (8%)	
Peripheral Vascular Disease Events	2 (<1%)	5 (2%)	5 (2%)	
Venous Disease Events	4 (2%)	3 (1%)	3 (1%)	
Hypertension Events	39 (17%)	27 (12%)	44 (20%)	
Other Cardiovascular Events	12 (5%)	10 (5%)	11 (5%)	
Participants with Unilateral Study Anti-VEGF Treatment at any time during the study				
Events occurring at least once (No. Participants)	**Aflibercept (N = 80)**	**Bevacizumab (N = 84)**	**Ranibizumab (N = 86)**	
Any Cardiovascular Event,† excluding Hypertension	13 (16%)	18 (21%)	23 (27%)	
Any Cardiovascular Event†	21 (26%)	22 (26%)	28 (33%)	
Cardiac Events	7 (9%)	12 (14%)	15 (17%)	
Cerebrovascular Events	1 (1%)	3 (4%)	9 (10%)	
Peripheral Vascular Disease Events	2 (3%)	0	4 (5%)	
Venous Disease Events	2 (3%)	1 (1%)	1 (1%)	
Hypertension Events	10 (13%)	6 (7%)	10 (12%)	
Other Cardiovascular Events	4 (5%)	4 (5%)	1 (1%)	
Participants with Bilateral Study Anti-VEGF Treatment at any time during the study				
Events occurring at least once (No. Participants)	**Aflibercept (N = 144)**	**Bevacizumab (N = 134)**	**Ranibizumab (N = 132)**	
Any Cardiovascular Event,† excluding Hypertension	31 (22%)	31 (23%)	36 (27%)	
Any Cardiovascular Event †	48 (33%)	47 (35%)	54 (41%)	
Cardiac Events	23 (16%)	22 (16%)	26 (20%)	
Cerebrovascular Events	3 (2%)	5 (4%)	9 (7%)	
Peripheral Vascular Disease Events	0	5 (4%)	1 (<1%)	
Venous Disease Events	2 (1%)	2 (1%)	2 (2%)	
Hypertension Events	29 (20%)	21 (16%)	34 (26%)	
Other Cardiovascular Events	8 (6%)	6 (4%)	10 (8%)	

*Global (overall 3 group comparison) P-value from Fisher's Exact Test. Global P-value from Poisson model with robust variance estimation using the log link[4] adjusting for for gender, age at baseline, Hemoglobin A1c at baseline, diabetes type, diabetes duration at baseline, insulin use, prior coronary artery disease, prior myocardial infarction, prior stroke, prior transient ischemic attack, prior hypertension, smoking status: P=0.26.

‡Global (overall 3 group comparison) P-value from Fisher's Exact Test. Global P-value from Poisson model with robust variance estimation using the log link[4] adjusting for gender, age at baseline, Hemoglobin A1c at baseline, diabetes type, diabetes duration at baseline, insulin use, prior coronary artery disease, prior myocardial infarction, prior stroke, prior transient ischemic attack, prior hypertension, smoking status: P=0.41.

† Includes events with a Medical Dictionary for Regulatory Activities system organ class of cardiac disorder or vascular disorder as coded by the medical monitor. The following additional events not coded under these systems but related to a cardiac or vascular event or intervention are also included in the cardiovascular definition: cardiac murmur, cardiac pacemaker insertion/replacement, coronary arterial stent insertion, heart rate irregular, heart transplant, implantable defibrillator insertion, stent placement, and troponin increased. Participants with multiple events are only included once in the overall tabulation but could be included in more than one of the subcategories.

Table S13. All Ocular Events Occurring in the Study Eye

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Anterior chamber			
Anterior chamber cell	2 (2)	1 (1)	3 (2)
Anterior chamber opacity	1 (1)	0 (0)	0 (0)
Flat anterior chamber of eye	0 (0)	1 (1)	1 (1)
Foreign body in anterior chamber	0 (0)	1 (1)	0 (0)
Choroid			
Choroidal neovascularisation	1 (1)	1 (1)	0 (0)
Conjunctiva			
Conjunctival haemorrhage	55 (34)	88 (41)	45 (26)
Conjunctival hyperaemia	0 (0)	1 (1)	2 (2)
Conjunctival oedema	3 (2)	0 (0)	0 (0)
Conjunctivitis	4 (4)	0 (0)	2 (2)
Conjunctivitis allergic	0 (0)	3 (3)	2 (2)
Conjunctivitis viral	0 (0)	0 (0)	1 (1)
Eye discharge	1 (1)	2 (2)	1 (1)
Ocular hyperaemia	0 (0)	8 (8)	11 (11)
Pinguecula	0 (0)	0 (0)	1 (1)
Cornea			
Corneal abrasion	6 (3)	11 (10)	7 (7)
Corneal disorder	1 (1)	0 (0)	4 (3)
Corneal erosion	1 (1)	0 (0)	0 (0)
Corneal oedema	1 (1)	0 (0)	1 (1)
Corneal opacity	1 (1)	0 (0)	0 (0)
Corneal pigmentation	2 (2)	0 (0)	0 (0)
Corneal scar	1 (1)	0 (0)	0 (0)
Keratitis	0 (0)	2 (2)	0 (0)
Keratitis sicca	1 (1)	0 (0)	0 (0)
Keratopathy	1 (1)	0 (0)	0 (0)
Punctate keratitis	10 (6)	2 (2)	5 (4)
External			
Arthropod bite	0 (0)	0 (0)	1 (1)
Dry eye	23 (20)	12 (12)	20 (20)
Dry eye syndrome	2 (2)	2 (2)	2 (2)
Eye infection	1 (1)	0 (0)	0 (0)
Eye irritation	25 (16)	27 (17)	23 (15)
Eye swelling	1 (1)	4 (3)	2 (2)
Hypersensitivity	1 (1)	0 (0)	0 (0)
Lacrimation increased	17 (15)	6 (6)	13 (11)
Ocular discomfort	6 (4)	4 (4)	6 (5)
Ophthalmic herpes simplex	0 (0)	1 (1)	0 (0)
Periorbital contusion	0 (0)	2 (2)	0 (0)
Seasonal allergy	0 (0)	0 (0)	1 (1)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Glaucoma-IOP			
Angle closure glaucoma	0 (0)	0 (0)	1 (1)
Borderline glaucoma	1 (1)	0 (0)	1 (1)
Glaucoma	0 (0)	1 (1)	4 (3)
Intraocular pressure increased	8 (8)	2 (2)	9 (7)
Ocular hypertension	2 (2)	6 (5)	2 (2)
Inflammation			
Anterior chamber flare	1 (1)	0 (0)	1 (1)
Choroiditis	0 (0)	1 (1)	0 (0)
Episcleritis	1 (1)	0 (0)	1 (1)
Iritis	5 (3)	1 (1)	1 (1)
Injection-related			
Injection site irritation	0 (0)	0 (0)	1 (1)
Iris			
Post procedural complication	0 (0)	1 (1)	0 (0)
Lens			
Cataract	31 (28)	22 (20)	17 (13)
Cataract cortical	3 (3)	2 (2)	4 (4)
Cataract nuclear	2 (2)	4 (4)	3 (3)
Cataract operation	3 (3)	1 (1)	7 (7)
Cataract operation complication	0 (0)	1 (1)	0 (0)
Cataract subcapsular	17 (17)	6 (6)	10 (10)
Posterior capsule opacification	8 (8)	6 (6)	5 (4)
Lids			
Blepharal papilloma	1 (1)	0 (0)	2 (2)
Blepharitis	7 (6)	2 (2)	4 (4)
Chalazion	1 (1)	0 (0)	0 (0)
Cutis laxa	1 (1)	2 (2)	0 (0)
Dermatitis contact	2 (1)	0 (0)	0 (0)
Ecchymosis	0 (0)	0 (0)	1 (1)
Eyelid margin crusting	3 (3)	1 (1)	0 (0)
Eyelid oedema	1 (1)	1 (1)	1 (1)
Eyelid ptosis	1 (1)	0 (0)	1 (1)
Eyelid twitching	1 (1)	1 (1)	2 (2)
Hordeolum	2 (2)	1 (1)	2 (2)
Papilloma	0 (0)	2 (2)	0 (0)
Trichiasis	1 (1)	1 (1)	0 (0)
Miscellaneous-eye			
Asthenopia	1 (1)	0 (0)	1 (1)
Blepharospasm	0 (0)	1 (1)	0 (0)
Fatigue	0 (0)	1 (1)	0 (0)
Optic nerve			
Optic atrophy	1 (1)	0 (0)	0 (0)
Optic disc disorder	1 (1)	0 (0)	1 (1)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Optic nerve cupping	1 (1)	0 (0)	0 (0)
Retina			
Chorioretinal atrophy	1 (1)	1 (1)	1 (1)
Cystoid macular oedema	0 (0)	1 (1)	1 (1)
Diabetic retinal oedema	4 (4)	4 (4)	2 (2)
Diabetic retinopathy	1 (1)	5 (4)	1 (1)
Macular fibrosis	8 (8)	11 (10)	2 (2)
Macular hole	0 (0)	1 (1)	0 (0)
Macular ischaemia	2 (2)	2 (2)	1 (1)
Macular oedema	1 (1)	0 (0)	1 (1)
Maculopathy	0 (0)	2 (2)	0 (0)
Retinal aneurysm	0 (0)	0 (0)	1 (1)
Retinal artery embolism	1 (1)	2 (2)	2 (2)
Retinal cyst	0 (0)	0 (0)	1 (1)
Retinal degeneration	0 (0)	0 (0)	1 (1)
Retinal detachment	2 (2)	2 (2)	1 (1)
Retinal disorder	0 (0)	3 (3)	0 (0)
Retinal exudates	8 (8)	6 (6)	5 (4)
Retinal haemorrhage	3 (3)	7 (6)	6 (6)
Retinal ischaemia	0 (0)	2 (2)	1 (1)
Retinal neovascularisation	2 (2)	2 (2)	2 (1)
Retinal pigment epitheliopathy	1 (1)	0 (0)	0 (0)
Retinal tear	1 (1)	1 (1)	1 (1)
Retinal vascular disorder	0 (0)	0 (0)	3 (3)
Retinal vein occlusion	0 (0)	1 (1)	1 (1)
Retinopathy	1 (1)	1 (1)	2 (2)
Retinopathy hypertensive	1 (1)	1 (1)	0 (0)
Vitreous adhesions	2 (2)	2 (2)	1 (1)
Sensation-pain			
Abnormal sensation in eye	0 (0)	1 (1)	1 (1)
Eye injury	0 (0)	1 (1)	0 (0)
Eye pain	35 (25)	44 (32)	23 (23)
Eye pruritus	14 (11)	14 (11)	19 (16)
Eyelid pain	1 (1)	3 (3)	0 (0)
Facial pain	1 (1)	0 (0)	0 (0)
Foreign body sensation in eyes	6 (5)	8 (6)	7 (6)
Headache	0 (0)	1 (1)	1 (1)
Pain	0 (0)	1 (1)	2 (1)
Strabismus			
Strabismus	0 (0)	1 (1)	0 (0)
Visual field			
Scotoma	0 (0)	2 (2)	0 (0)
Visual field defect	0 (0)	1 (1)	0 (0)
Visual symptoms/abnormality			

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Altered visual depth perception	0 (0)	2 (2)	0 (0)
Colour blindness acquired	0 (0)	1 (1)	0 (0)
Diplopia	6 (6)	3 (3)	9 (9)
Glare	1 (1)	3 (3)	3 (3)
Halo vision	1 (1)	0 (0)	0 (0)
Metamorphopsia	6 (4)	7 (7)	2 (2)
Migraine with aura	1 (1)	1 (1)	1 (1)
Night blindness	1 (1)	1 (1)	0 (0)
Photophobia	7 (7)	5 (5)	4 (4)
Photopsia	7 (6)	5 (5)	11 (9)
Reading disorder	0 (0)	1 (1)	0 (0)
Vision blurred	65 (54)	58 (51)	69 (50)
Visual acuity reduced	26 (22)	29 (27)	29 (22)
Visual impairment	15 (12)	11 (11)	14 (10)
Vitreous			
Endophthalmitis	0 (0)	1 (1)	0 (0)
Hyalosis asteroid	0 (0)	0 (0)	1 (1)
Vitreal cells	1 (1)	0 (0)	1 (1)
Vitreous degeneration	1 (1)	4 (3)	1 (1)
Vitreous detachment	9 (9)	16 (15)	10 (9)
Vitreous disorder	0 (0)	0 (0)	1 (1)
Vitreous floaters	51 (41)	71 (54)	61 (49)
Vitreous haemorrhage	17 (15)	27 (17)	13 (10)
Vitreous opacities	0 (0)	1 (1)	0 (0)

Events based on medical monitor using Medical Dictionary for Regulatory Activities coding.

Table S14. All Ocular Adverse Events Occurring in the Non-Study Eye from the First Non-Study Eye Injection

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Anterior chamber			
Anterior chamber cell	0 (0)	1 (1)	1 (1)
Conjunctiva			
Conjunctival haemorrhage	30 (13)	49 (17)	16 (8)
Conjunctival hyperaemia	0 (0)	1 (1)	0 (0)
Conjunctivitis	0 (0)	1 (1)	0 (0)
Conjunctivitis allergic	1 (1)	0 (0)	0 (0)
Eye discharge	1 (1)	1 (1)	0 (0)
Ocular hyperaemia	0 (0)	2 (2)	0 (0)
Pinguecula	0 (0)	0 (0)	1 (1)
Pterygium	0 (0)	1 (1)	0 (0)
Cornea			
Corneal abrasion	2 (2)	8 (5)	0 (0)
Corneal defect	0 (0)	0 (0)	1 (1)
Corneal disorder	0 (0)	0 (0)	1 (1)
Corneal dystrophy	1 (1)	0 (0)	0 (0)
Corneal erosion	0 (0)	0 (0)	1 (1)
Corneal irritation	0 (0)	2 (2)	0 (0)
Corneal oedema	1 (1)	0 (0)	3 (2)
Corneal scar	1 (1)	0 (0)	0 (0)
Keratitis	0 (0)	1 (1)	0 (0)
Punctate keratitis	3 (3)	1 (1)	0 (0)
External			
Arthropod sting	1 (1)	0 (0)	0 (0)
Dry eye	9 (8)	9 (9)	10 (10)
Dry eye syndrome	0 (0)	1 (1)	0 (0)
Eye infection	1 (1)	0 (0)	0 (0)
Eye irritation	14 (8)	9 (6)	12 (9)
Eye swelling	0 (0)	1 (1)	0 (0)
Lacrimation increased	10 (10)	1 (1)	5 (5)
Ocular discomfort	3 (1)	3 (3)	6 (4)
Ophthalmic herpes simplex	0 (0)	2 (1)	0 (0)
Periorbital contusion	0 (0)	1 (1)	1 (1)
Seasonal allergy	0 (0)	0 (0)	1 (1)
Glaucoma-IOP			
Angle closure glaucoma	0 (0)	0 (0)	1 (1)
Borderline glaucoma	1 (1)	0 (0)	1 (1)
Glaucoma	0 (0)	0 (0)	4 (4)
Hypotony of eye	1 (1)	0 (0)	0 (0)
Intraocular pressure increased	3 (3)	4 (3)	4 (4)
Ocular hypertension	2 (2)	2 (2)	1 (1)
Inflammation			

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Anterior chamber flare	1 (1)	1 (1)	0 (0)
Iritis	1 (1)	1 (1)	1 (1)
Iris			
Iris adhesions	1 (1)	0 (0)	0 (0)
Iris neovascularisation	0 (0)	1 (1)	0 (0)
Lens			
Cataract	15 (14)	12 (12)	6 (6)
Cataract cortical	2 (2)	3 (3)	1 (1)
Cataract nuclear	1 (1)	2 (2)	2 (2)
Cataract operation	2 (2)	1 (1)	1 (1)
Cataract operation complication	0 (0)	0 (0)	1 (1)
Cataract subcapsular	6 (6)	3 (3)	6 (6)
Posterior capsule opacification	6 (5)	3 (3)	6 (5)
Lids			
Acrochordon	0 (0)	0 (0)	1 (1)
Blepharitis	2 (2)	1 (1)	4 (4)
Chalazion	1 (1)	1 (1)	0 (0)
Cutis laxa	0 (0)	1 (1)	0 (0)
Ecchymosis	1 (1)	0 (0)	0 (0)
Eyelid margin crusting	1 (1)	1 (1)	0 (0)
Eyelid oedema	1 (1)	0 (0)	1 (1)
Hordeolum	2 (1)	2 (2)	0 (0)
Papilloma	0 (0)	1 (1)	0 (0)
Skin lesion	0 (0)	0 (0)	1 (1)
Miscellaneous-eye			
Fatigue	0 (0)	1 (1)	0 (0)
Optic nerve			
Optic atrophy	1 (1)	1 (1)	1 (1)
Optic nerve cupping	1 (1)	0 (0)	0 (0)
Papilloedema	1 (1)	0 (0)	0 (0)
Retina			
Chorioretinal atrophy	0 (0)	1 (1)	0 (0)
Cystoid macular oedema	0 (0)	0 (0)	2 (2)
Diabetic retinal oedema	12 (10)	8 (8)	10 (10)
Diabetic retinopathy	2 (2)	2 (2)	7 (7)
Eye naevus	0 (0)	0 (0)	1 (1)
Macular degeneration	0 (0)	0 (0)	1 (1)
Macular fibrosis	5 (5)	9 (8)	2 (2)
Macular hole	0 (0)	2 (1)	0 (0)
Macular ischaemia	0 (0)	1 (1)	0 (0)
Macular oedema	3 (3)	0 (0)	2 (2)
Retinal aneurysm	2 (1)	1 (1)	1 (1)
Retinal disorder	0 (0)	1 (1)	0 (0)
Retinal exudates	4 (4)	7 (7)	4 (4)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Retinal haemorrhage	5 (5)	2 (2)	7 (7)
Retinal ischaemia	0 (0)	1 (1)	0 (0)
Retinal laser coagulation	1 (1)	1 (1)	1 (1)
Retinal neovascularisation	5 (4)	0 (0)	0 (0)
Retinal tear	0 (0)	0 (0)	2 (2)
Retinal vascular disorder	1 (1)	0 (0)	1 (1)
Retinal vein occlusion	0 (0)	1 (1)	0 (0)
Retinopathy	1 (1)	1 (1)	0 (0)
Retinopathy hypertensive	1 (1)	0 (0)	0 (0)
Vitreous adhesions	1 (1)	0 (0)	1 (1)
Sensation-pain			
Eye contusion	0 (0)	0 (0)	1 (1)
Eye pain	14 (10)	20 (17)	11 (7)
Eye pruritus	5 (3)	4 (4)	15 (12)
Eyelid pain	0 (0)	1 (1)	0 (0)
Foreign body sensation in eyes	3 (3)	3 (3)	1 (1)
Headache	1 (1)	0 (0)	2 (2)
Pain	0 (0)	2 (2)	0 (0)
Visual field			
Visual field defect	1 (1)	1 (1)	0 (0)
Visual symptoms/abnormality			
Altered visual depth perception	0 (0)	2 (2)	0 (0)
Diplopia	1 (1)	0 (0)	7 (7)
Glare	2 (2)	0 (0)	1 (1)
Halo vision	1 (1)	0 (0)	0 (0)
Metamorphopsia	0 (0)	4 (4)	2 (2)
Migraine with aura	1 (1)	0 (0)	0 (0)
Photophobia	7 (7)	1 (1)	4 (3)
Photopsia	5 (5)	6 (6)	6 (4)
Reading disorder	0 (0)	1 (1)	0 (0)
Vision blurred	38 (30)	21 (21)	43 (37)
Visual acuity reduced	12 (9)	12 (9)	16 (12)
Visual impairment	5 (5)	9 (7)	5 (3)
Vitreous			
Endophthalmitis	2 (1)	0 (0)	1 (1)
Foreign body in vitreous	0 (0)	1 (1)	0 (0)
Vitreal cells	1 (1)	1 (1)	0 (0)
Vitrectomy	0 (0)	0 (0)	1 (1)
Vitreous degeneration	0 (0)	3 (2)	1 (1)
Vitreous detachment	7 (7)	6 (6)	2 (2)
Vitreous floaters	34 (25)	24 (20)	30 (22)
Vitreous haemorrhage	14 (11)	18 (12)	10 (9)

Events based on medical monitor using Medical Dictionary for Regulatory Activities coding.

Table S15. All Systemic Adverse Events

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Blood and lymphatic system disorders			
Anaemia	21 (20)	11 (11)	16 (15)
Anaemia of chronic disease	4 (4)	8 (8)	2 (2)
Coagulopathy	0 (0)	1 (1)	0 (0)
Leukocytosis	1 (1)	1 (1)	0 (0)
Lymphadenitis	0 (0)	1 (1)	0 (0)
Lymphadenopathy	2 (2)	0 (0)	0 (0)
Lymphangitis	1 (1)	0 (0)	0 (0)
Lymphoedema	2 (2)	0 (0)	0 (0)
Lymphoma	0 (0)	0 (0)	1 (1)
Pancytopenia	0 (0)	1 (1)	0 (0)
Plasma cell myeloma	0 (0)	0 (0)	1 (1)
Thrombocytopenia	0 (0)	2 (1)	0 (0)
Cardiac disorders			
Acute coronary syndrome	0 (0)	0 (0)	1 (1)
Angina pectoris	1 (1)	2 (2)	1 (1)
Angina unstable	0 (0)	1 (1)	0 (0)
Arrhythmia	1 (1)	0 (0)	0 (0)
Arteriosclerosis coronary artery	2 (2)	0 (0)	1 (1)
Atrial fibrillation	4 (4)	3 (3)	5 (5)
Atrial flutter	0 (0)	0 (0)	2 (2)
Atrioventricular block first degree	1 (1)	0 (0)	0 (0)
Atrioventricular block second degree	0 (0)	0 (0)	2 (2)
Bradycardia	0 (0)	1 (1)	5 (4)
Bundle branch block	0 (0)	3 (3)	0 (0)
Cardiac arrest	0 (0)	3 (3)	2 (2)
Cardiac failure	0 (0)	1 (1)	3 (3)
Cardiac failure congestive	12 (11)	20 (11)	17 (12)
Cardiomegaly	1 (1)	1 (1)	0 (0)
Cardiomyopathy	2 (2)	0 (0)	2 (2)
Coronary artery disease	4 (4)	7 (7)	8 (8)
Diabetic cardiomyopathy	0 (0)	1 (1)	0 (0)
Diastolic dysfunction	2 (1)	1 (1)	2 (2)
Hypertensive heart disease	3 (2)	2 (2)	1 (1)
Mitral valve calcification	0 (0)	1 (1)	0 (0)
Mitral valve incompetence	0 (0)	3 (3)	0 (0)
Mitral valve stenosis	0 (0)	1 (1)	0 (0)
Myocardial infarction	7 (7)	4 (4)	9 (9)
Palpitations	0 (0)	0 (0)	2 (2)
Pericardial effusion	1 (1)	1 (1)	2 (1)
Pericarditis	0 (0)	0 (0)	1 (1)
Supraventricular tachycardia	1 (1)	0 (0)	0 (0)
Tachycardia	3 (2)	1 (1)	0 (0)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Tricuspid valve incompetence	0 (0)	0 (0)	1 (1)
Ventricular hypokinesia	0 (0)	0 (0)	1 (1)
Ventricular tachycardia	0 (0)	0 (0)	3 (3)
Wolff-Parkinson-White syndrome	0 (0)	0 (0)	1 (1)
Ear and labyrinth disorders			
Cerumen impaction	2 (2)	0 (0)	0 (0)
Deafness	0 (0)	3 (3)	0 (0)
Ear infection	8 (8)	3 (3)	1 (1)
Ear pain	0 (0)	1 (1)	1 (1)
Tinnitus	1 (1)	2 (2)	0 (0)
Endocrine disorders			
Adrenal mass	0 (0)	1 (1)	0 (0)
Autoimmune thyroiditis	1 (1)	0 (0)	0 (0)
Diabetes mellitus	7 (6)	5 (5)	8 (7)
Diabetes mellitus inadequate control	16 (15)	21 (19)	15 (14)
Diabetic ketoacidosis	2 (2)	3 (3)	2 (2)
Glucocorticoid deficiency	1 (1)	0 (0)	0 (0)
Hyperglycaemia	8 (5)	4 (4)	5 (5)
Hyperglycaemic hyperosmolar nonketotic syndrome	0 (0)	0 (0)	1 (1)
Hyperthyroidism	1 (1)	1 (1)	1 (1)
Hypoglycaemia	16 (13)	12 (11)	12 (11)
Hypothyroidism	8 (8)	1 (1)	4 (4)
Thyroid neoplasm	0 (0)	1 (1)	0 (0)
Thyroiditis	0 (0)	1 (1)	0 (0)
Gastrointestinal disorders			
Abdominal discomfort	5 (5)	8 (8)	2 (2)
Abdominal distension	1 (1)	0 (0)	1 (1)
Abdominal pain	7 (5)	6 (4)	6 (5)
Abdominal pain upper	2 (2)	3 (3)	3 (3)
Barrett's oesophagus	1 (1)	0 (0)	0 (0)
Clostridium difficile colitis	2 (2)	1 (1)	4 (3)
Colitis ischaemic	0 (0)	2 (2)	0 (0)
Colitis microscopic	0 (0)	1 (1)	0 (0)
Colitis ulcerative	0 (0)	2 (2)	0 (0)
Colon cancer	0 (0)	1 (1)	2 (2)
Colorectal cancer	0 (0)	0 (0)	1 (1)
Constipation	7 (7)	12 (11)	8 (8)
Dental caries	1 (1)	1 (1)	1 (1)
Diabetic gastroparesis	2 (2)	1 (1)	1 (1)
Diarrhoea	11 (9)	18 (15)	15 (13)
Diverticulum	1 (1)	1 (1)	2 (2)
Duodenitis	0 (0)	1 (1)	0 (0)
Dyspepsia	2 (2)	4 (4)	3 (3)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Dysphagia	1 (1)	0 (0)	0 (0)
Faecal incontinence	0 (0)	0 (0)	1 (1)
Gastric cancer stage I	0 (0)	0 (0)	1 (1)
Gastric ulcer	0 (0)	3 (3)	2 (2)
Gastritis	0 (0)	2 (2)	2 (2)
Gastroenteritis	1 (1)	5 (5)	2 (2)
Gastroenteritis viral	12 (10)	8 (7)	14 (13)
Gastrointestinal haemorrhage	2 (2)	3 (2)	3 (2)
Gastrointestinal stoma complication	0 (0)	0 (0)	1 (1)
Gastrooesophageal reflux disease	14 (14)	9 (9)	3 (3)
Haematochezia	1 (1)	0 (0)	1 (1)
Haemorrhoids	3 (3)	1 (1)	1 (1)
Hiatus hernia	0 (0)	1 (1)	1 (1)
Impaired gastric emptying	1 (1)	0 (0)	5 (3)
Intestinal obstruction	0 (0)	1 (1)	0 (0)
Intestinal perforation	0 (0)	2 (2)	0 (0)
Irritable bowel syndrome	1 (1)	0 (0)	0 (0)
Large intestine polyp	3 (3)	1 (1)	1 (1)
Nausea	13 (12)	18 (12)	15 (13)
Oesophageal varices haemorrhage	0 (0)	2 (1)	0 (0)
Oesophagitis	4 (4)	0 (0)	1 (1)
Pancreatitis	1 (1)	1 (1)	1 (1)
Peptic ulcer	0 (0)	1 (1)	1 (1)
Rectal haemorrhage	2 (2)	0 (0)	0 (0)
Rectal ulcer	0 (0)	0 (0)	1 (1)
Tooth abscess	3 (3)	2 (2)	5 (5)
Tooth fracture	2 (2)	1 (1)	0 (0)
Tooth impacted	0 (0)	1 (1)	0 (0)
Tooth infection	3 (3)	3 (3)	2 (2)
Toothache	4 (4)	1 (1)	1 (1)
Vomiting	24 (17)	14 (9)	11 (10)
General disorders and administration site conditions			
Chest discomfort	1 (1)	0 (0)	6 (6)
Chest pain	10 (7)	11 (9)	9 (6)
Chills	1 (1)	0 (0)	2 (2)
Cyst	5 (4)	3 (3)	2 (2)
Death	3 (3)	4 (4)	4 (4)
Device related infection	1 (1)	2 (2)	0 (0)
Facial pain	0 (0)	3 (3)	0 (0)
Fatigue	12 (11)	10 (9)	2 (2)
Flank pain	1 (1)	0 (0)	0 (0)
Generalised oedema	0 (0)	0 (0)	2 (2)
Hernia	0 (0)	1 (1)	0 (0)
Hot flush	1 (1)	0 (0)	0 (0)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Hypothermia	1 (1)	0 (0)	0 (0)
Lethargy	0 (0)	2 (2)	1 (1)
Local swelling	4 (4)	1 (1)	2 (2)
Necrosis	0 (0)	1 (1)	1 (1)
Oedema peripheral	12 (11)	10 (10)	14 (11)
Pain	6 (6)	6 (5)	8 (7)
Pyrexia	3 (3)	7 (6)	5 (4)
Swelling	4 (4)	4 (4)	3 (3)
Hepatobiliary disorders			
Cholecystitis acute	0 (0)	1 (1)	3 (3)
Cholecystitis chronic	1 (1)	1 (1)	0 (0)
Cholelithiasis	2 (2)	2 (2)	0 (0)
Hepatic cirrhosis	1 (1)	6 (3)	0 (0)
Hepatic encephalopathy	0 (0)	2 (1)	0 (0)
Hepatic failure	0 (0)	1 (1)	0 (0)
Porcelain gallbladder	0 (0)	1 (1)	0 (0)
Immune system disorders			
Drug hypersensitivity	1 (1)	1 (1)	1 (1)
Heart transplant rejection	0 (0)	1 (1)	0 (0)
Hypersensitivity	3 (3)	4 (3)	1 (1)
Immune thrombocytopenic purpura	0 (0)	1 (1)	0 (0)
Seasonal allergy	14 (14)	11 (11)	11 (11)
Urticaria	0 (0)	1 (1)	1 (1)
Infections and infestations			
Abscess	5 (4)	1 (1)	1 (1)
Bacteraemia	0 (0)	0 (0)	1 (1)
Blister infected	1 (1)	0 (0)	0 (0)
Candida infection	0 (0)	1 (1)	0 (0)
Diverticulitis	2 (2)	1 (1)	0 (0)
Escherichia infection	0 (0)	1 (1)	1 (1)
Fungal infection	3 (3)	0 (0)	1 (1)
Fungal skin infection	1 (1)	1 (1)	1 (1)
Gingival infection	0 (0)	0 (0)	1 (1)
Gingivitis	0 (0)	1 (1)	0 (0)
Helicobacter infection	1 (1)	1 (1)	0 (0)
Infection	4 (4)	15 (12)	9 (9)
Influenza	18 (16)	18 (17)	21 (20)
Localised infection	7 (6)	19 (15)	12 (9)
Oral herpes	1 (1)	0 (0)	0 (0)
Post procedural infection	0 (0)	1 (1)	0 (0)
Postoperative wound infection	1 (1)	0 (0)	1 (1)
Sepsis	4 (4)	4 (4)	4 (4)
Septic shock	0 (0)	1 (1)	0 (0)
Staphylococcal infection	4 (3)	0 (0)	2 (2)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Streptococcal infection	0 (0)	2 (2)	0 (0)
Viral infection	1 (1)	1 (1)	0 (0)
Injury, poisoning and procedural complications			
Accidental overdose	0 (0)	0 (0)	1 (1)
Animal bite	1 (1)	0 (0)	1 (1)
Arthropod bite	2 (2)	0 (0)	2 (2)
Arthropod sting	4 (3)	0 (0)	0 (0)
Asbestosis	1 (1)	0 (0)	0 (0)
Burns second degree	0 (0)	1 (1)	1 (1)
Chemical injury	0 (0)	0 (0)	1 (1)
Fall	14 (12)	24 (16)	14 (11)
Fibula fracture	1 (1)	0 (0)	0 (0)
Head injury	0 (0)	2 (2)	1 (1)
Heat exhaustion	0 (0)	0 (0)	1 (1)
Injury	1 (1)	0 (0)	0 (0)
Joint injury	4 (4)	1 (1)	0 (0)
Laceration	2 (2)	3 (3)	5 (5)
Limb injury	2 (2)	3 (3)	3 (3)
Post procedural complication	0 (0)	1 (1)	0 (0)
Pulmonary contusion	1 (1)	0 (0)	0 (0)
Skin injury	0 (0)	1 (1)	0 (0)
Spinal fracture	0 (0)	1 (1)	0 (0)
Subgaleal haematoma	1 (1)	0 (0)	0 (0)
Thermal burn	1 (1)	2 (2)	3 (3)
Tibia fracture	2 (2)	0 (0)	0 (0)
Wound	2 (1)	2 (2)	0 (0)
Investigations			
Biopsy lymph gland	0 (0)	1 (1)	0 (0)
Biopsy skin	0 (0)	0 (0)	1 (1)
Blood creatine increased	0 (0)	2 (2)	2 (2)
Blood creatinine abnormal	3 (3)	3 (3)	2 (2)
Blood glucose decreased	3 (3)	4 (4)	6 (5)
Blood glucose increased	2 (2)	2 (2)	1 (1)
Blood lactic acid increased	0 (0)	1 (1)	0 (0)
Blood potassium decreased	1 (1)	3 (3)	0 (0)
Blood potassium increased	2 (2)	2 (2)	5 (5)
Blood testosterone decreased	2 (2)	0 (0)	1 (1)
Cardiac murmur	0 (0)	3 (3)	0 (0)
Colonoscopy	1 (1)	0 (0)	0 (0)
Glycosylated haemoglobin increased	0 (0)	0 (0)	1 (1)
Haematocrit abnormal	0 (0)	0 (0)	1 (1)
Haemoglobin decreased	0 (0)	1 (1)	0 (0)
Heart rate increased	1 (1)	0 (0)	0 (0)
Heart rate irregular	0 (0)	1 (1)	0 (0)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Hepatic enzyme increased	1 (1)	0 (0)	2 (2)
International normalised ratio increased	4 (3)	0 (0)	1 (1)
Laboratory test abnormal	2 (2)	2 (2)	4 (2)
Low density lipoprotein increased	1 (1)	0 (0)	1 (1)
Mammogram abnormal	1 (1)	0 (0)	0 (0)
Mean cell haemoglobin increased	0 (0)	1 (1)	0 (0)
Monocyte count increased	0 (0)	1 (1)	0 (0)
Protein urine present	3 (3)	2 (2)	1 (1)
Red blood cell count decreased	1 (1)	1 (1)	1 (1)
Troponin increased	1 (1)	2 (2)	1 (1)
Weight decreased	1 (1)	0 (0)	1 (1)
Metabolism and nutrition disorders			
Abnormal weight gain	2 (2)	0 (0)	1 (1)
Acidosis	0 (0)	1 (1)	1 (1)
Calciphylaxis	0 (0)	1 (1)	0 (0)
Decreased appetite	1 (1)	3 (3)	0 (0)
Dehydration	11 (8)	4 (4)	13 (11)
Failure to thrive	0 (0)	0 (0)	1 (1)
Fluid overload	1 (1)	1 (1)	4 (2)
Fluid retention	3 (3)	4 (4)	2 (2)
Haemochromatosis	0 (0)	0 (0)	1 (1)
Hypercalcaemia	0 (0)	1 (1)	0 (0)
Hypercholesterolaemia	15 (15)	9 (9)	10 (10)
Hyperkalaemia	6 (6)	4 (4)	4 (4)
Hyperlipidaemia	8 (8)	5 (5)	5 (4)
Hypermagnesaemia	0 (0)	0 (0)	1 (1)
Hyperphosphataemia	2 (2)	2 (2)	3 (3)
Hypertriglyceridaemia	1 (1)	1 (1)	1 (1)
Hypoalbuminaemia	0 (0)	0 (0)	1 (1)
Hypocalcaemia	0 (0)	0 (0)	1 (1)
Hypokalaemia	3 (3)	2 (2)	1 (1)
Hypomagnesaemia	0 (0)	0 (0)	3 (3)
Hyponatraemia	1 (1)	1 (1)	0 (0)
Iron deficiency	1 (1)	1 (1)	3 (3)
Magnesium deficiency	0 (0)	1 (1)	0 (0)
Malnutrition	0 (0)	2 (2)	0 (0)
Metabolic disorder	1 (1)	1 (1)	1 (1)
Obesity	1 (1)	1 (1)	2 (2)
Type 2 diabetes mellitus	1 (1)	0 (0)	0 (0)
Vitamin B12 deficiency	0 (0)	1 (1)	1 (1)
Vitamin D deficiency	4 (4)	1 (1)	13 (12)
Musculoskeletal and connective tissue disorders			
Ankle fracture	2 (2)	0 (0)	2 (2)
Arthralgia	9 (9)	8 (7)	13 (11)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Arthritis	2 (2)	2 (2)	4 (4)
Back pain	15 (13)	21 (19)	21 (17)
Bone pain	0 (0)	1 (1)	0 (0)
Bursitis	1 (1)	1 (1)	2 (2)
Clavicle fracture	1 (1)	0 (0)	0 (0)
Coccydynia	0 (0)	2 (2)	0 (0)
Dupuytren's contracture	0 (0)	3 (2)	0 (0)
Exostosis	2 (2)	1 (1)	1 (1)
Facial bones fracture	0 (0)	0 (0)	1 (1)
Femoral neck fracture	0 (0)	1 (1)	0 (0)
Femur fracture	0 (0)	1 (1)	0 (0)
Fibromyalgia	1 (1)	0 (0)	2 (2)
Foot deformity	0 (0)	1 (1)	3 (2)
Foot fracture	7 (7)	4 (4)	0 (0)
Fractured coccyx	0 (0)	1 (1)	0 (0)
Gout	1 (1)	4 (4)	1 (1)
Hand fracture	2 (2)	0 (0)	2 (1)
Hip fracture	1 (1)	1 (1)	1 (1)
Inclusion body myositis	1 (1)	0 (0)	0 (0)
Intervertebral disc degeneration	0 (0)	3 (3)	0 (0)
Intervertebral disc protrusion	1 (1)	3 (2)	1 (1)
Ligament sprain	7 (6)	4 (3)	9 (8)
Lipoma	0 (0)	1 (1)	0 (0)
Lower limb fracture	1 (1)	1 (1)	1 (1)
Meniscus injury	0 (0)	2 (2)	1 (1)
Multiple fractures	4 (4)	3 (3)	5 (5)
Muscle spasms	6 (6)	9 (9)	2 (2)
Muscle strain	1 (1)	2 (2)	3 (3)
Muscular weakness	6 (6)	4 (4)	7 (7)
Musculoskeletal discomfort	2 (2)	2 (2)	0 (0)
Musculoskeletal pain	4 (4)	9 (9)	6 (6)
Myalgia	1 (1)	4 (3)	1 (1)
Neck pain	1 (1)	3 (3)	4 (4)
Neuropathic arthropathy	2 (1)	2 (2)	1 (1)
Osteoarthritis	2 (2)	3 (3)	5 (5)
Osteomyelitis	3 (3)	6 (5)	5 (5)
Osteoporosis	0 (0)	3 (3)	0 (0)
Pain in extremity	7 (6)	14 (11)	9 (9)
Pelvic fracture	2 (2)	0 (0)	0 (0)
Plantar fasciitis	2 (2)	0 (0)	1 (1)
Psoriatic arthropathy	0 (0)	0 (0)	1 (1)
Rhabdomyolysis	0 (0)	0 (0)	1 (1)
Rheumatoid arthritis	1 (1)	3 (2)	0 (0)
Rib fracture	2 (2)	2 (2)	2 (2)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Rotator cuff syndrome	2 (2)	0 (0)	2 (2)
Spinal osteoarthritis	1 (1)	0 (0)	0 (0)
Tendon disorder	0 (0)	1 (1)	0 (0)
Tendonitis	5 (5)	0 (0)	2 (2)
Trigger finger	3 (3)	1 (1)	3 (3)
Upper limb fracture	2 (2)	1 (1)	2 (2)
Wrist fracture	3 (3)	3 (3)	1 (1)
Neoplasms benign, malignant and unspecified(incl cysts and polyps)			
Hepatic cancer	1 (1)	0 (0)	0 (0)
Lung cancer metastatic	1 (1)	0 (0)	0 (0)
Neoplasm	1 (1)	0 (0)	0 (0)
Neoplasm malignant	0 (0)	1 (1)	0 (0)
Polyp	1 (1)	2 (2)	4 (3)
Squamous cell carcinoma	2 (1)	2 (1)	2 (2)
Nervous system disorders			
Amnesia	0 (0)	2 (2)	0 (0)
Ataxia	0 (0)	1 (1)	0 (0)
Balance disorder	3 (2)	3 (3)	2 (2)
Brain neoplasm	0 (0)	0 (0)	2 (2)
Carpal tunnel syndrome	5 (2)	1 (1)	1 (1)
Cerebral atrophy	1 (1)	0 (0)	0 (0)
Concussion	0 (0)	0 (0)	1 (1)
Convulsion	0 (0)	1 (1)	12 (5)
Dementia	0 (0)	0 (0)	2 (2)
Dementia Alzheimer's type	0 (0)	2 (2)	0 (0)
Diabetic neuropathy	3 (3)	9 (9)	6 (6)
Dizziness	15 (13)	7 (7)	16 (14)
Dysarthria	1 (1)	0 (0)	0 (0)
Encephalopathy	2 (2)	4 (2)	2 (2)
Epilepsy	0 (0)	0 (0)	1 (1)
Gait disturbance	1 (1)	0 (0)	0 (0)
Head discomfort	0 (0)	0 (0)	1 (1)
Headache	26 (20)	27 (19)	23 (20)
Hemiparesis	2 (2)	0 (0)	0 (0)
Hydrocephalus	0 (0)	0 (0)	1 (1)
Hypoaesthesia	1 (1)	2 (2)	2 (2)
Hypogeusia	0 (0)	1 (1)	0 (0)
Meningioma	0 (0)	0 (0)	1 (1)
Migraine	8 (7)	2 (2)	2 (2)
Multiple sclerosis	0 (0)	0 (0)	1 (1)
Nerve compression	0 (0)	2 (2)	0 (0)
Nerve injury	1 (1)	1 (1)	1 (1)
Neuropathy peripheral	5 (5)	6 (6)	10 (9)
Paraesthesia	1 (1)	1 (1)	0 (0)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Presyncope	2 (2)	4 (3)	2 (2)
Radiculitis brachial	0 (0)	0 (0)	1 (1)
Restless legs syndrome	2 (2)	0 (0)	1 (1)
Sciatica	3 (3)	1 (1)	3 (3)
Seizure	0 (0)	0 (0)	2 (2)
Somnolence	1 (1)	1 (1)	0 (0)
Spinal column stenosis	2 (2)	0 (0)	1 (1)
Syncope	1 (1)	1 (1)	9 (9)
Tremor	0 (0)	0 (0)	1 (1)
VIIth nerve paralysis	5 (4)	0 (0)	2 (2)
Vertigo	9 (8)	6 (5)	3 (3)
Vestibular neuronitis	1 (1)	0 (0)	0 (0)
Psychiatric disorders			
Affect lability	0 (0)	0 (0)	1 (1)
Anxiety	9 (9)	10 (8)	7 (7)
Bipolar disorder	1 (1)	0 (0)	3 (2)
Delirium	0 (0)	1 (1)	0 (0)
Depression	11 (11)	12 (10)	8 (7)
Drug abuse	0 (0)	0 (0)	1 (1)
Insomnia	5 (4)	6 (6)	4 (4)
Mental disorder	2 (2)	6 (3)	2 (2)
Panic attack	1 (1)	1 (1)	0 (0)
Psychotic disorder	0 (0)	0 (0)	3 (2)
Schizoaffective disorder	0 (0)	0 (0)	1 (1)
Stress	0 (0)	2 (2)	0 (0)
Renal and urinary disorders			
Acute kidney injury	1 (1)	2 (2)	1 (1)
Acute prerenal failure	0 (0)	0 (0)	1 (1)
Azotaemia	0 (0)	0 (0)	1 (1)
Bladder cancer	0 (0)	1 (1)	0 (0)
Bladder prolapse	0 (0)	0 (0)	1 (1)
Bladder spasm	0 (0)	0 (0)	1 (1)
Chronic kidney disease	3 (3)	0 (0)	5 (5)
Cystitis	9 (7)	3 (2)	2 (2)
Cystitis haemorrhagic	1 (1)	0 (0)	0 (0)
Diabetic nephropathy	0 (0)	1 (1)	0 (0)
Dysuria	1 (1)	0 (0)	0 (0)
Glomerulonephritis membranous	0 (0)	1 (1)	0 (0)
Haematuria	1 (1)	8 (8)	1 (1)
Hydronephrosis	0 (0)	0 (0)	1 (1)
Hypertonic bladder	1 (1)	1 (1)	0 (0)
Kidney infection	2 (2)	1 (1)	4 (4)
Microalbuminuria	2 (2)	0 (0)	0 (0)
Micturition urgency	0 (0)	0 (0)	3 (3)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Nephrolithiasis	4 (4)	3 (3)	3 (3)
Nephropathy	4 (4)	4 (4)	2 (2)
Nephrotic syndrome	1 (1)	0 (0)	0 (0)
Proteinuria	2 (2)	3 (3)	1 (1)
Renal cyst	2 (2)	0 (0)	0 (0)
Renal disorder	0 (0)	1 (1)	0 (0)
Renal failure	12 (12)	17 (13)	14 (12)
Renal failure acute	6 (5)	8 (7)	7 (7)
Renal failure chronic	15 (14)	10 (8)	15 (10)
Renal impairment	7 (7)	4 (4)	3 (3)
Urinary hesitation	0 (0)	1 (1)	0 (0)
Urinary incontinence	1 (1)	1 (1)	2 (2)
Urinary retention	0 (0)	1 (1)	1 (1)
Urinary tract infection	25 (17)	30 (22)	13 (12)
Reproductive system and breast disorders			
Benign prostatic hyperplasia	2 (2)	0 (0)	1 (1)
Breast cancer	0 (0)	1 (1)	0 (0)
Endometrial hyperplasia	0 (0)	2 (1)	0 (0)
Erectile dysfunction	0 (0)	1 (1)	2 (2)
Fibrocystic breast disease	0 (0)	0 (0)	1 (1)
Ovarian neoplasm	1 (1)	0 (0)	0 (0)
Penile necrosis	0 (0)	0 (0)	1 (1)
Prostatitis	0 (0)	0 (0)	2 (2)
Prostatomegaly	1 (1)	2 (2)	3 (3)
Uterine leiomyoma	3 (3)	0 (0)	0 (0)
Uterine prolapse	0 (0)	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	3 (3)	2 (2)	5 (5)
Asthma	6 (5)	3 (3)	2 (2)
Atelectasis	1 (1)	2 (2)	0 (0)
Bronchitis	15 (12)	22 (13)	13 (11)
Cardio-respiratory arrest	0 (0)	1 (1)	0 (0)
Chronic obstructive pulmonary disease	1 (1)	4 (3)	2 (2)
Chronic respiratory disease	0 (0)	1 (1)	0 (0)
Chronic sinusitis	1 (1)	1 (1)	1 (1)
Cough	23 (22)	14 (11)	17 (14)
Dyspnoea	10 (9)	15 (10)	12 (10)
Epistaxis	5 (2)	1 (1)	2 (2)
Haemoptysis	0 (0)	0 (0)	1 (1)
Hiccups	0 (0)	0 (0)	1 (1)
Hypercapnia	1 (1)	0 (0)	0 (0)
Hypoxia	0 (0)	4 (4)	2 (2)
Laryngitis	1 (1)	0 (0)	0 (0)
Nasal congestion	6 (6)	8 (7)	4 (4)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Nasal dryness	1 (1)	0 (0)	0 (0)
Nasopharyngitis	46 (39)	49 (38)	35 (29)
Obstructive airways disorder	0 (0)	1 (1)	0 (0)
Oropharyngeal pain	3 (3)	8 (8)	4 (4)
Pharyngitis streptococcal	2 (2)	1 (1)	0 (0)
Pleural effusion	0 (0)	1 (1)	0 (0)
Pneumonia	12 (9)	18 (17)	22 (18)
Pneumonia aspiration	0 (0)	1 (1)	0 (0)
Pulmonary embolism	0 (0)	0 (0)	2 (2)
Pulmonary fibrosis	1 (1)	0 (0)	0 (0)
Pulmonary hypertension	0 (0)	1 (1)	1 (1)
Pulmonary oedema	0 (0)	2 (1)	3 (3)
Respiratory distress	0 (0)	0 (0)	1 (1)
Respiratory tract congestion	0 (0)	2 (2)	1 (1)
Respiratory tract infection	4 (4)	2 (2)	3 (2)
Respiratory tract oedema	0 (0)	1 (1)	0 (0)
Rhinalgia	1 (1)	0 (0)	0 (0)
Rhinitis allergic	1 (1)	5 (5)	2 (2)
Rhinorrhoea	0 (0)	1 (1)	0 (0)
Sinusitis	22 (20)	14 (13)	31 (18)
Sleep apnoea syndrome	3 (3)	4 (4)	3 (3)
Sneezing	1 (1)	0 (0)	0 (0)
Upper respiratory tract infection	21 (15)	11 (10)	25 (19)
Upper-airway cough syndrome	0 (0)	1 (1)	0 (0)
Wheezing	2 (2)	0 (0)	2 (2)
Skin and subcutaneous tissue disorders			
Acne	2 (1)	0 (0)	0 (0)
Actinic keratosis	0 (0)	0 (0)	2 (1)
Alopecia	1 (1)	1 (1)	3 (3)
Angioedema	0 (0)	0 (0)	1 (1)
Basal cell carcinoma	5 (5)	2 (2)	2 (2)
Blister	1 (1)	2 (2)	0 (0)
Cellulitis	14 (12)	17 (14)	13 (12)
Cellulitis gangrenous	0 (0)	1 (1)	0 (0)
Contusion	3 (3)	4 (3)	1 (1)
Dermal cyst	1 (1)	0 (0)	1 (1)
Dermatitis allergic	2 (2)	1 (1)	1 (1)
Dermatitis contact	2 (1)	1 (1)	0 (0)
Diabetic foot	2 (2)	8 (7)	10 (8)
Diabetic ulcer	0 (0)	1 (1)	1 (1)
Ecchymosis	1 (1)	0 (0)	1 (1)
Eczema	0 (0)	0 (0)	1 (1)
Excoriation	3 (3)	3 (3)	1 (1)
Furuncle	5 (3)	1 (1)	7 (3)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Gangrene	1 (1)	2 (1)	2 (2)
Herpes zoster	2 (2)	1 (1)	3 (3)
Hyperhidrosis	0 (0)	0 (0)	2 (2)
Hyperkeratosis	1 (1)	4 (4)	0 (0)
Ingrowing nail	0 (0)	4 (3)	0 (0)
Malignant melanoma	0 (0)	1 (1)	0 (0)
Melanocytic naevus	1 (1)	0 (0)	1 (1)
Nail avulsion	0 (0)	0 (0)	1 (1)
Night sweats	1 (1)	0 (0)	0 (0)
Onychogryphosis	0 (0)	1 (1)	0 (0)
Onychomycosis	1 (1)	1 (1)	1 (1)
Pruritus	2 (2)	2 (2)	0 (0)
Psoriasis	0 (0)	1 (1)	0 (0)
Rash	6 (5)	4 (4)	3 (3)
Skin abrasion	1 (1)	1 (1)	0 (0)
Skin bacterial infection	1 (1)	2 (2)	1 (1)
Skin cancer	0 (0)	2 (2)	2 (2)
Skin disorder	0 (0)	0 (0)	1 (1)
Skin infection	8 (8)	1 (1)	2 (2)
Skin lesion	1 (1)	0 (0)	3 (2)
Skin papilloma	1 (1)	0 (0)	2 (1)
Skin ulcer	5 (5)	2 (2)	2 (2)
Social circumstances			
Menopause	0 (0)	1 (1)	0 (0)
Surgical and medical procedures			
Cardiac pacemaker insertion	0 (0)	1 (1)	1 (1)
Cardiac pacemaker replacement	1 (1)	0 (0)	0 (0)
Cataract operation	0 (0)	0 (0)	1 (1)
Cholecystectomy	0 (0)	3 (3)	1 (1)
Coronary arterial stent insertion	0 (0)	2 (2)	0 (0)
Cystopexy	0 (0)	1 (1)	0 (0)
Dental implantation	0 (0)	1 (1)	0 (0)
Endodontic procedure	0 (0)	1 (1)	1 (1)
Foot amputation	0 (0)	1 (1)	0 (0)
Gastric bypass	1 (1)	0 (0)	0 (0)
Heart transplant	0 (0)	1 (1)	0 (0)
Hip arthroplasty	0 (0)	0 (0)	1 (1)
Hyperbaric oxygen therapy	0 (0)	1 (1)	0 (0)
Implantable defibrillator insertion	0 (0)	0 (0)	1 (1)
Inguinal hernia repair	1 (1)	0 (0)	0 (0)
Knee operation	0 (0)	0 (0)	1 (1)
Leg amputation	0 (0)	2 (2)	1 (1)
Sinus operation	0 (0)	1 (1)	0 (0)
Skin lesion excision	1 (1)	0 (0)	0 (0)

No. Events (No. Participants)	Aflibercept	Bevacizumab	Ranibizumab
Stent placement	2 (2)	2 (2)	0 (0)
Surgery	2 (2)	2 (2)	6 (4)
Toe amputation	0 (0)	1 (1)	2 (2)
Tooth extraction	6 (6)	5 (4)	4 (4)
Uterine dilation and curettage	1 (1)	0 (0)	0 (0)
Vitrectomy	1 (1)	0 (0)	0 (0)
Vascular disorders			
Aortic aneurysm	0 (0)	1 (1)	0 (0)
Aortic stenosis	1 (1)	1 (1)	0 (0)
Arteriosclerosis	0 (0)	2 (2)	0 (0)
Arteriovenous fistula	4 (3)	1 (1)	6 (5)
Basilar artery occlusion	0 (0)	0 (0)	1 (1)
Carotid artery disease	0 (0)	0 (0)	1 (1)
Carotid artery stenosis	1 (1)	0 (0)	0 (0)
Cerebral infarction	0 (0)	0 (0)	1 (1)
Cerebrovascular accident	1 (1)	4 (4)	10 (8)
Deep vein thrombosis	2 (2)	3 (2)	1 (1)
Embolism	1 (1)	1 (1)	1 (1)
Haematoma	3 (3)	1 (1)	1 (1)
Haemorrhagic stroke	1 (1)	1 (1)	1 (1)
Hypertension	44 (39)	32 (26)	53 (44)
Hypertensive crisis	0 (0)	1 (1)	0 (0)
Hypotension	3 (3)	2 (2)	4 (4)
Ischaemia	0 (0)	0 (0)	1 (1)
Ischaemic stroke	0 (0)	1 (1)	5 (4)
Orthostatic hypotension	2 (2)	2 (2)	0 (0)
Peripheral ischaemia	0 (0)	0 (0)	1 (1)
Peripheral vascular disorder	3 (2)	5 (5)	3 (3)
Peripheral venous disease	1 (1)	0 (0)	0 (0)
Poor peripheral circulation	0 (0)	0 (0)	1 (1)
Raynaud's phenomenon	1 (1)	0 (0)	0 (0)
Transient ischaemic attack	1 (1)	3 (3)	7 (5)
Venous insufficiency	0 (0)	1 (1)	2 (1)
Venous stenosis	1 (1)	0 (0)	1 (1)

Events based on medical monitor using Medical Dictionary for Regulatory Activities coding.

Table S16. 2 Year Anti-Platelet Trialists' Collaboration (APTC) [5] Event Rates Across DME and AMD Studies Comparing Ranibizumab vs. Control or Other Anti-VEGF Agents

	Treatment Group									
Study	**Control (Laser or Sham)**		**Aflibercept 0.5 mg**		**Bevacizumab 1.25 mg**		**Ranibizumab 0.3 mg**		**Ranibizumab 0.5 mg**	
N participants in denominator / % of participants with at least one APTC event	N	%	N	%	N	%	N	%	N	%
DME Trials										
RISE/RIDE Pooled [6]	250	5.2%					250	5.6%	250	7.2%
RISE	123	4.9%					125	2.4%	126	8.7%
RIDE	127	5.5%					125	8.8%	124	5.6%
DRCR.net Protocol I[7]	130	13%							375	7%
DRCR.net Protocol T			224	5%	218	8%			218	12%
RESTORE [12]	110	4.5%							235	3.4%
CNV in AMD Trials										
IVAN[8]					296	3%			314	4%
CATT[9]					586	5.0%			599	4.7%
VIEW*[10]			601	3.8%					595	3.2%

*96 weeks instead of 2 years

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