Supplementary Appendix

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

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Contents

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Diabetic Retinopathy Clinical Research Network clinical sites that participated on this protocol:

Sites are listed in order by number of subjects enrolled into the study. The number of subjects enrolled is noted in parenthesis preceded by the site location and the site name. Personnel are listed as (I) for Study Investigator, (C) for Coordinator, (V) Visual Acuity Technician, and (P) for Photographer.

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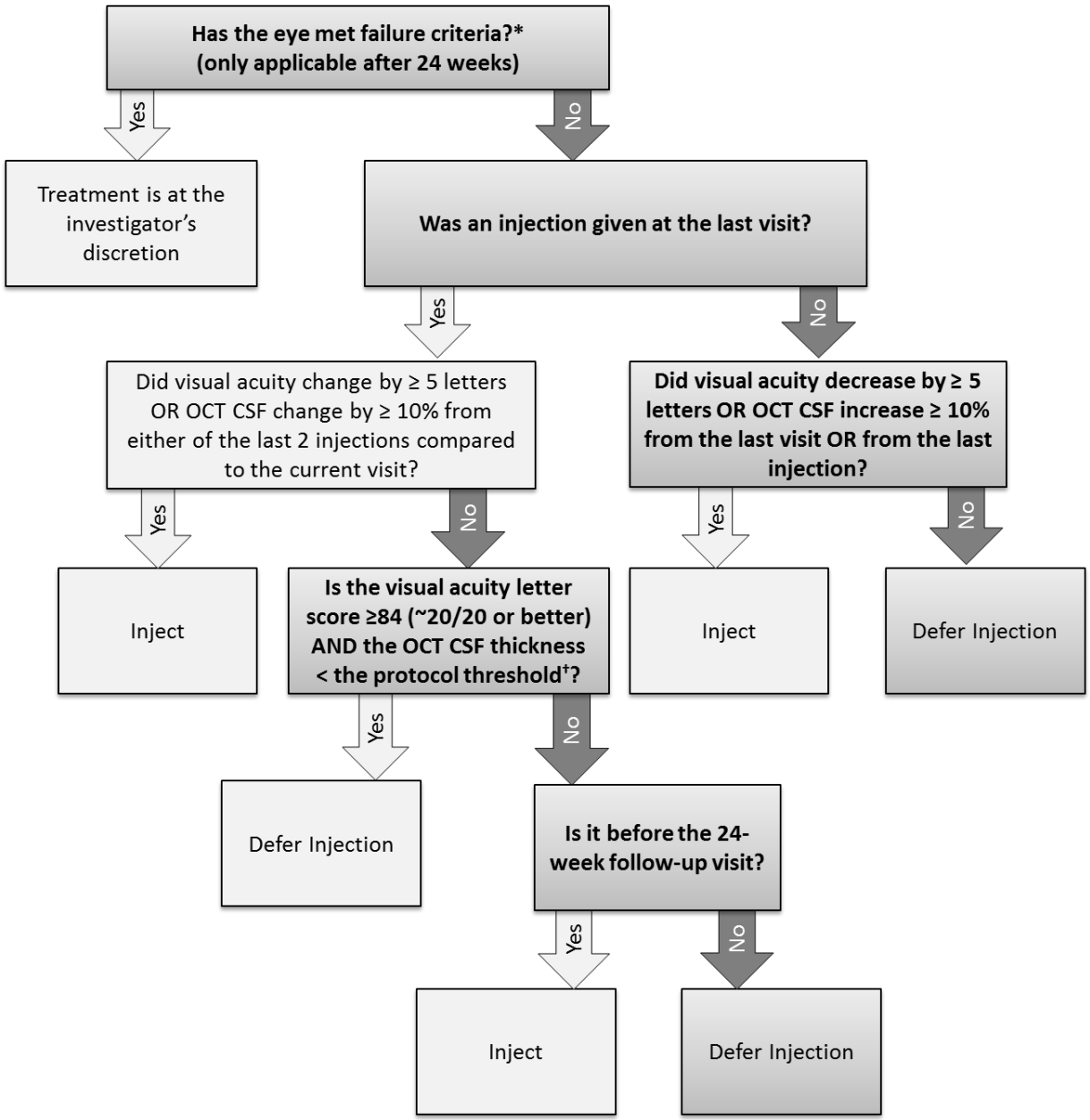
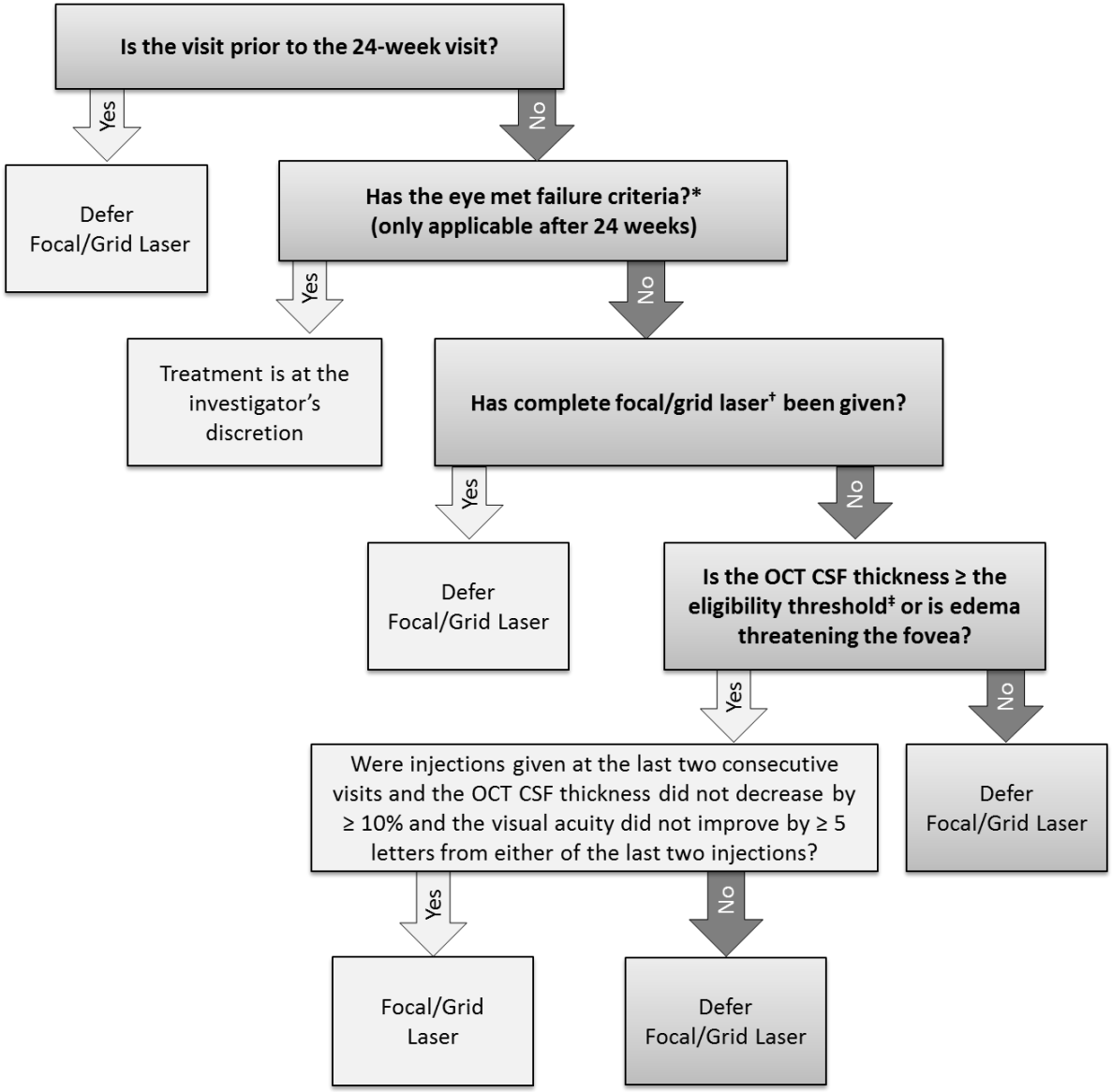
Figure S1A. Diabetic Macular Edema Treatment with anti-VEGF during Follow-up



OCT = optical coherence tomography, CSF = central subfield, DME = diabetic macular edema
*Failure = failure can only be met at or after the 24-week visit IF each of the following are met: A) OCT CSF thickness ≥ eligibility threshold B) visual acuity is 10 or more letters worse than baseline at 2 consecutive visits, C) DME present on clinical exam that the investigator believes is the cause of the visual acuity loss, D) complete focal/grid laser for DME has been given, E) there has been no improvement in visual acuity (>5 letters) or OCT (>10% OCT CSF thickness) since either of the last two injections, F) there has been no improvement in visual acuity (>5 letters) or OCT (>10% OCT CSF thickness)since the last focal/grid laser treatment for DME was given, AND G) it has been ≥13 weeks since the last focal/grid laser treatment for DME.
†Protocol threshold = >250 µm on Zeiss Stratus; ≥ 320 for men or ≥305 for women on Heidelberg Spectralis; ≥305 for men or ≥290 for women on Zeiss Cirrus.

Figure S1B. Initiating Focal/Grid Photocoagulation for Diabetic Macular Edema Treatment



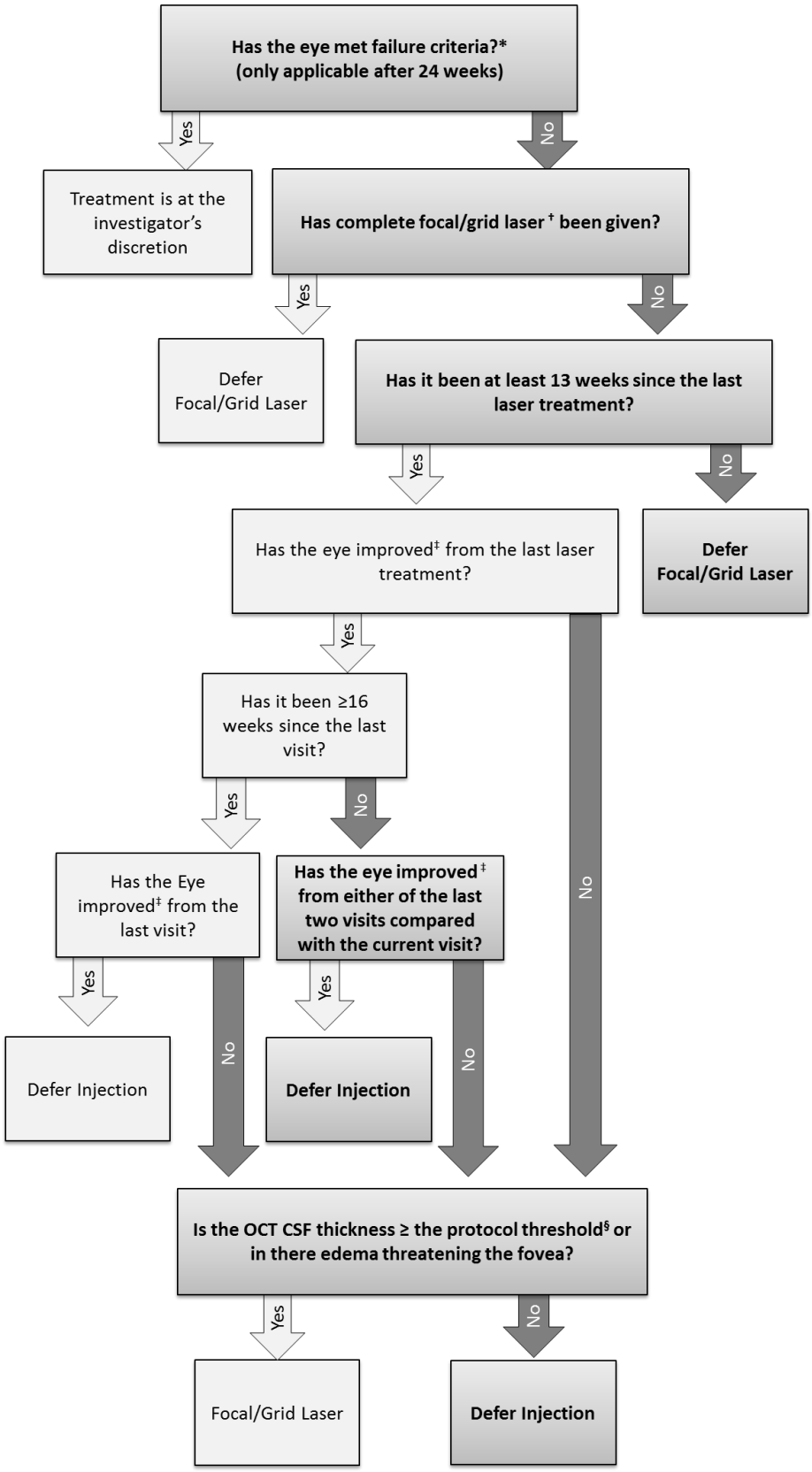
OCT = optical coherence tomography, CSF = central subfield, DME = diabetic macular edema

*Failure = can only be met at or after the 24-week visit IF each of the following are met: A) OCT CSF thickness ≥ the eligibility threshold, B) visual acuity is 10 or more letters worse than baseline at 2 consecutive visits, C) DME present on clinical examination that the investigator believes is the cause of the visual acuity loss, D) complete focal/grid laser for DME has been given, E) there has been no improvement in visual acuity (≥5 letters) or OCT (≥10% OCT CSF thickness) since either of the last two injections, F) there has been no improvement in visual acuity (>5 letters) or OCT (>10% OCT CSF thickness) since the last focal/grid laser treatment for DME was given, AND G) it has been ≥13 weeks since the last laser treatment.

†Complete focal/grid laser for DME = A) Beyond 500 µm of the foveal center all microaneurysms within areas of retinal thickening or contributing to the edema have been adequately and directly treated with laser burns directly over the microaneurysms AND all areas of current retinal thickening have been treated with laser burns, such that the laser burns are "on average" within 100 µm of each other (range between 50 and 150 microns) in a grid pattern throughout the area of retinal thickening, OR B) The ONLY untreated microaneurysms are within 300 to 500 µm of the foveal center with visual acuity better than 20/40 and the risks of additional focal/grid are judged to outweigh benefits OR the ONLY microaneurysms are within 300 µm of the foveal center, AND all other areas of macular thickening beyond 500 µm have been treated as described in A above.

‡Eligibility threshold = ≥250 µm on Zeiss Stratus; ≥ 320 for men or ≥305 for women on Heidelberg Spectralis; ≥305 for men or ≥290 for women on Zeiss Cirrus

Figure S1C. Re-Treatment with Focal/Grid Photocoagulation during Follow-up for Diabetic Macular Edema



OCT = optical coherence tomography, CSF = central subfield

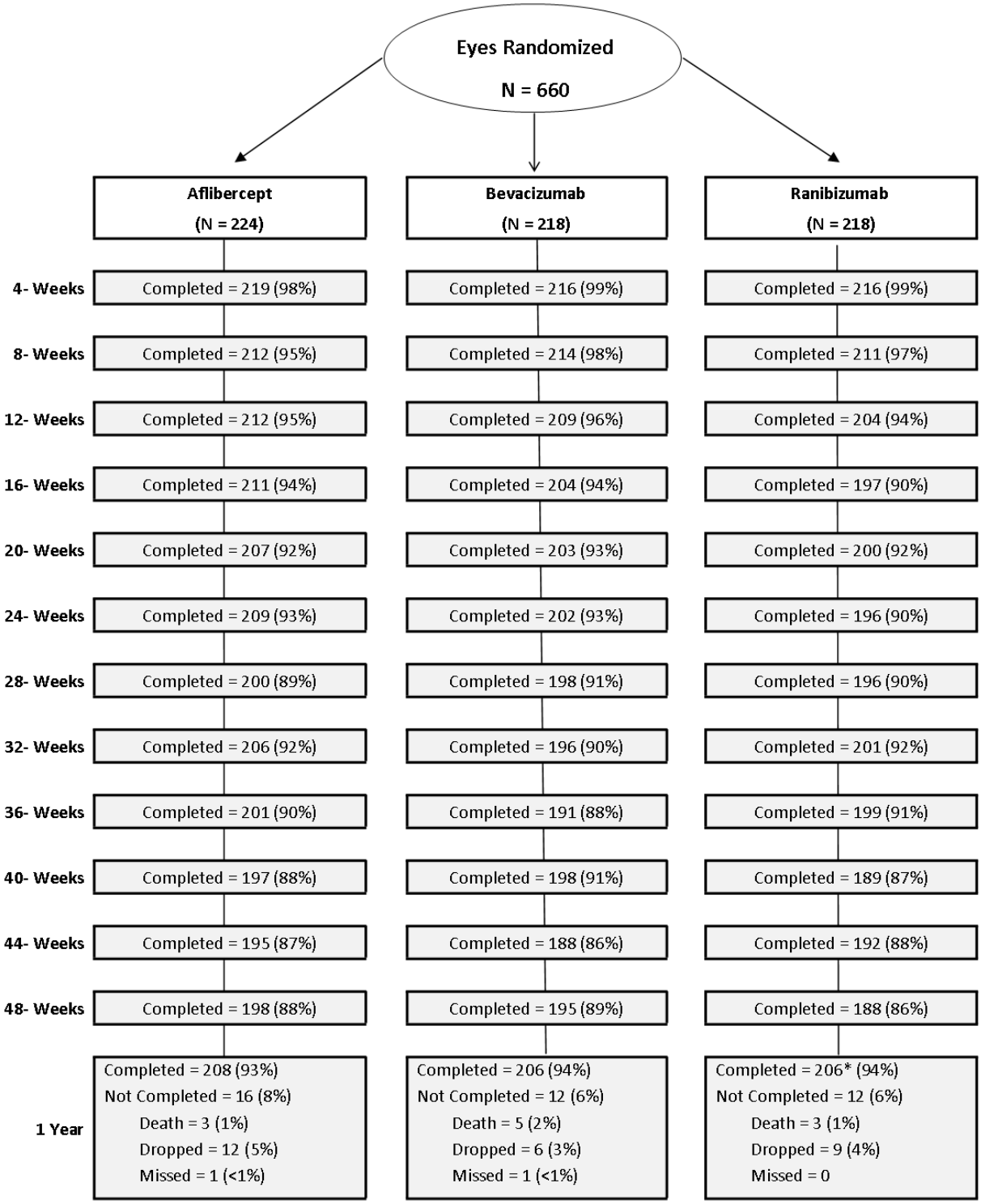
***Failure** = failure can only be met at or after the 24-week visit IF all of the following are met: A) OCT CSF thickness ≥ 250 µm on Zeiss Stratus; ≥ 320 for men or ≥305 for women on Heidelberg Spectralis; ≥305 for men or ≥290 for women on Zeiss Cirrus B) visual acuity is 10 or more letters worse than baseline at 2 consecutive visits, C) DME present of clinical exam that the investigator believes is the cause of the visual acuity loss, D) complete laser has been given, E) there has been no improvement since either of the last two injections, F)there has been no improvement since the last laser treatment was given, AND G) it has been ≥13 weeks since the last laser treatment.

†Complete focal/grid laser for DME = A) Beyond 500 µm of the foveal center all microaneurysms within areas of retinal thickening or contributing to the edema have been adequately and directly treated with laser burns directly over the microaneurysms AND all areas of current retinal thickening have been treated with laser burns, such that the laser burns are "on average" within 100 microns of each other (range between 50 and 150 microns) in a grid pattern throughout the area of retinal thickening OR B). The ONLY untreated microaneurysms are within 300 to 500 µm of the foveal center with visual acuity better than 20/40 and the risks of additional focal/grid are judged to outweigh benefits OR the ONLY microaneurysms are within 300 µm of the foveal center, AND all other areas of macular thickening beyond 500 µm have been treated as described in A above.

‡Improved = Optical coherence tomography central subfield thickness decreased by ≥ 10 or visual acuity letter score improved by ≥ 5

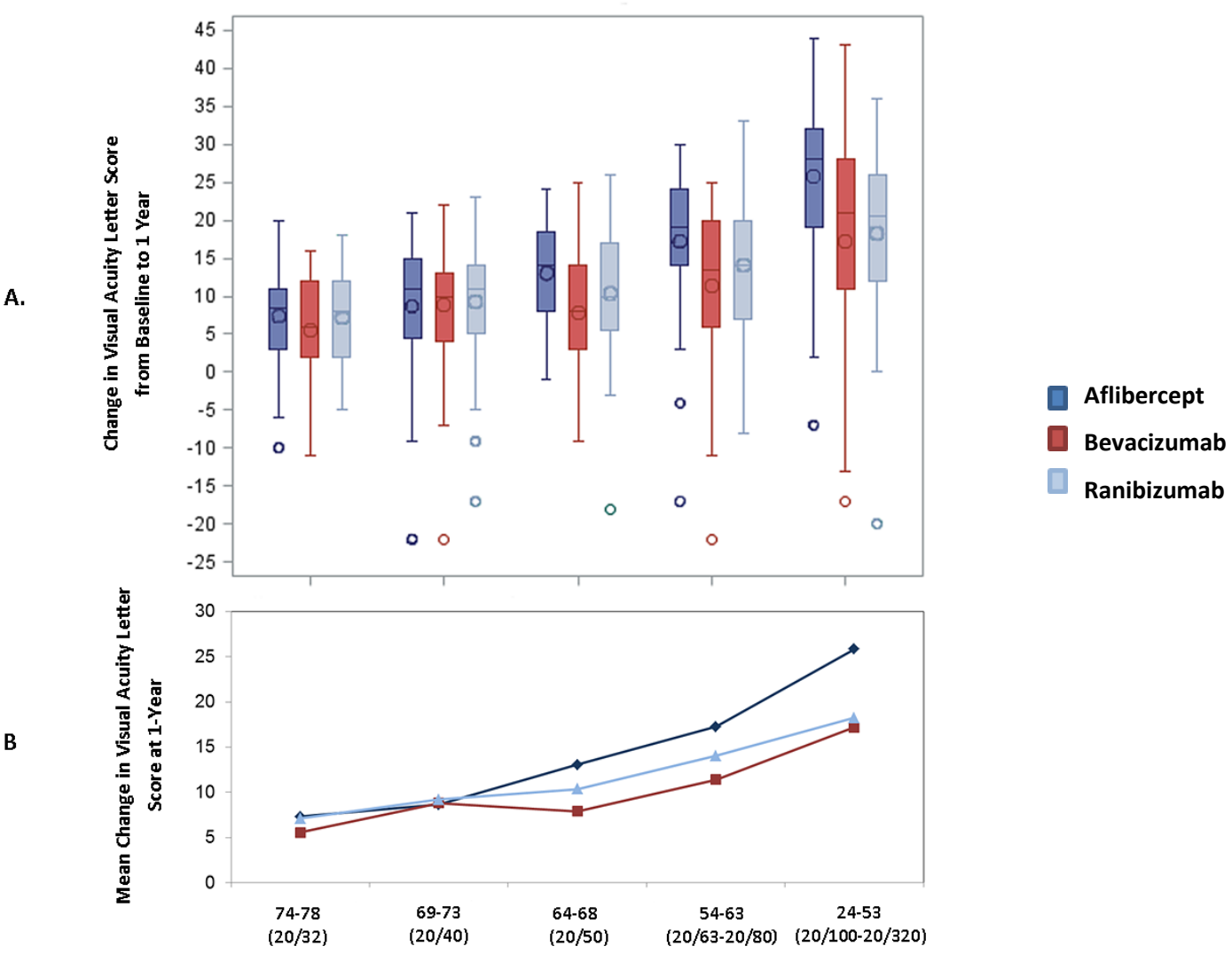
§Eligibility threshold = ≥250 µm on Zeiss Stratus; ≥ 320 for men or ≥305 for women on Heidelberg Spectralis; ≥305 for men or ≥290 for women on Zeiss Cirrus.

Figure S2. Completion of Follow-up for Study Eyes.*



*One-year completed visits include those that occurred between 308 and 420 days (between 44 and 60 weeks) from randomization. One death occurring after the 1 year visit but prior to 365 days is counted in the adverse event table but is not reflected in the flow chart.

Figure S3. Change in Visual Acuity from Baseline to 1 Year by Treatment Group According to Baseline Visual Acuity

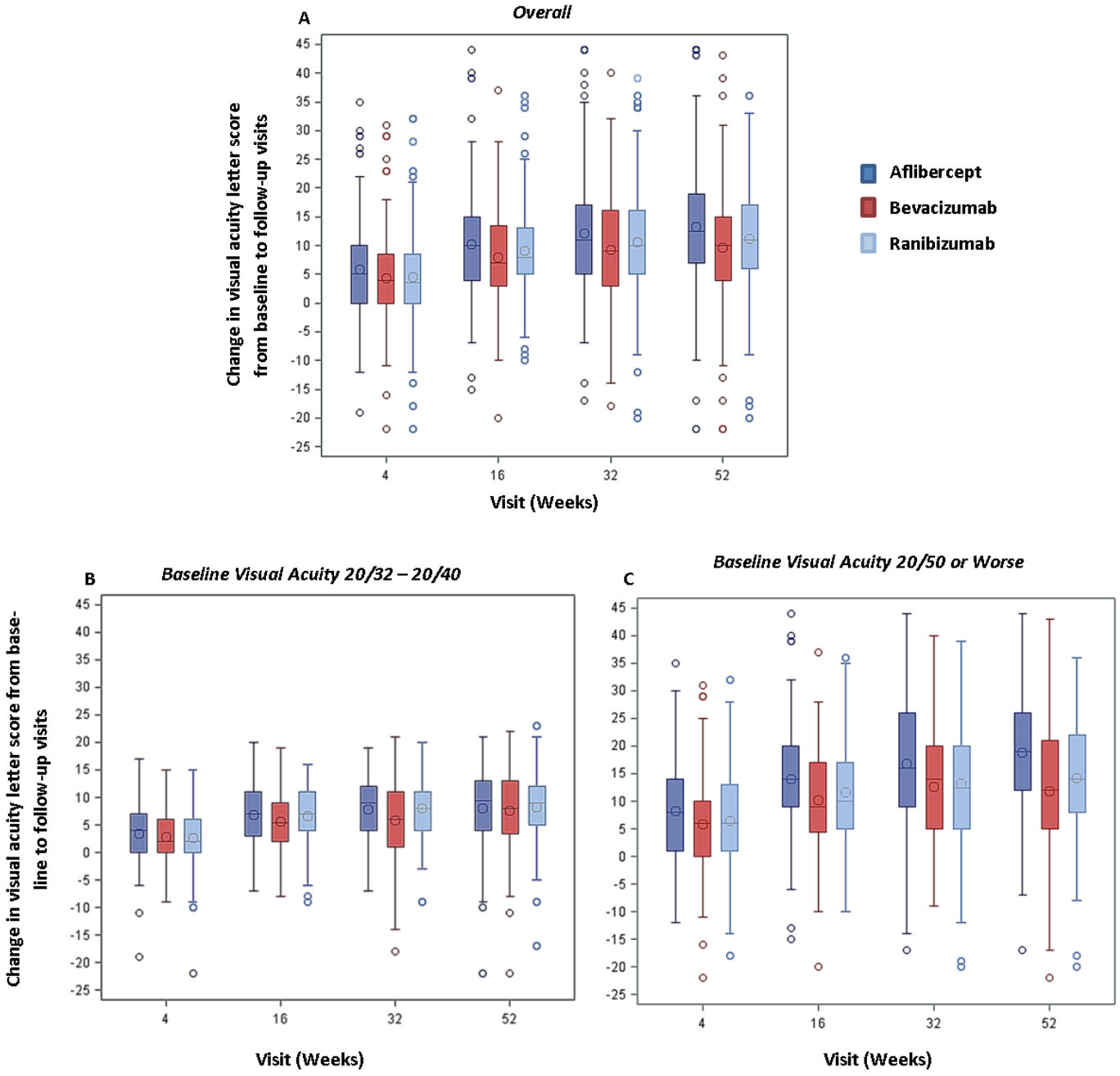


N* =					
Aflibercept	54	52	36	29	37
Bevacizumab	41	63	35	38	29
Ranibizumab	46	59	32	37	32

*Number of participants for figures A and B.

Change in visual acuity from baseline to 1 year, truncated to 3 standard deviations from the mean; stratified by baseline visual acuity. **Panel A:** Box plots showing distribution of 1-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 1 year.

Figure S4. Change in Visual Acuity Score from Baseline to Follow-up Visits



Box plots showing distribution of change in visual acuities from baseline to 4 weeks, 16 weeks, 32 weeks, and 1 year; 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. Change in visual acuity was truncated to 3 standard deviations from the mean. (Number at each 4-week visit [Figure S1]). **Panel A**: Overall, **Panel B**: baseline visual acuity (approximate Snellen equivalent): 20/32-20/40, **Panel C:** baseline visual acuity (approximate Snellen equivalent): 20/50 or worse.

Table S1. Eligibility Criteria	
	Participants
Inclusion	Age ≥ 18 years.
	Diagnosis of type 1 or type 2 diabetes.
Exclusion	Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant.
	A condition that, in the opinion of the investigator, would preclude participation (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control).
	Participation in an investigational trial within 30 days of randomization that involved treatment with any drug that has not received regulatory approval for the indication being studied at the time of study entry.
	Known allergy to any component of the study drug.
	Blood pressure > 180/110 (systolic above 180 OR diastolic above 110).
	Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 4 months prior to randomization.
	Systemic anti-VEGF or pro-VEGF treatment within four months prior to randomization or anticipated use during the study.
	For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 24 months.
	Individual is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the first 12 months of the study.
	Study Eye
Inclusion	Best corrected E-ETDRS visual acuity letter score ≤ 78 (20/32 or worse) and ≥ 24 (20/320 or better).
	Definite retinal thickening on clinical exam due to DME involving the center of the macula.
	Media clarity, pupillary dilation, and individual cooperation sufficient for adequate fundus photographs.
	Central subfield thickness on OCT ≥250 µm on Zeiss Stratus; ≥320 if male or ≥305 if female on Heidelberg Spectralis; ≥305 if male or ≥290 if female on Zeiss Cirrus.
Exclusion	Macular edema is considered to be due to a cause other than DME.
	An ocular condition is present such that, in the opinion of the investigator, visual acuity loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, or non-retinal condition).

	An ocular condition is present (other than diabetes) that might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.).
	A substantial cataract is present that is likely to be decreasing visual acuity by three lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal).
	History of an anti-VEGF treatment for DME in the past 12 months or history of any other treatment for DME at any time in the past four months (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids).
	History of panretinal photocoagulation within four months prior to randomization or anticipated need for pan-retinal photocoagulation in the six months following randomization.
	History of anti-VEGF treatment for a disease other than DME in the past 12 months.
	History of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior four months or anticipated within the next six months following randomization.
	History of YAG capsulotomy performed within two months prior to randomization.
	Aphakia
	Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis.

VEGF = vascular endothelial growth factor, E-ETDRS = Electronic- Early Treatment Diabetic Retinopathy Study, DME = diabetic macular edema, OCT = Optical coherence tomography

Table S2. Study Bevacizumab Potency Testing Process and Results
1. Between May 2012 and October 2014 the University of Pennsylvania, Investigational Drug Service produced six separate batches of repackaged bevacizumab used for this trial.
2. A sample of 20 vials from each batch was sent to an independent lab for potency testing. The contents of the vials were pooled for each batch for potency measurement.
3. The potency concentration from each of the 6 batches was: 25.1 mg/mL, 26.4 mg/mL, 24.8 mg/mL, 25.3 mg/mL, 25.2 mg/mL, and 25.0 mg/mL.
4. At the time of potency assessment for each batch, the independent testing lab also measured the potency of one unaltered commercially available vial of bevacizumab. The potency of this assessment was 25 mg/mL for each run. This value is consistent with the expected potency concentration based on prior publications.[1]

Table S3. Visual Acuity at 1 Year: Sensitivity Analysis			
	P values adjusted for multiple comparisons via Hochberg method[2]		
Method Used	**Aflibercept vs Bevacizumab**	**Aflibercept vs Ranibizumab**	**Ranibizumab vs Bevacizumab**
Primary Analysis: Markov chain Monte Carlo method of multiple imputation[3] (100 imputations) used to estimate missing 1 year change in visual acuity*	P<0.001	P=0.034	P=0.12
Multiple imputation dataset used in primary analysis, adjusting for potential confounders (any prior DME treatment, age, baseline central subfield thickness, diabetes type, baseline lens status, and baseline Hemoglobin A1c)*	P<0.001	P=0.031	P=0.17
Observed data only*	P<0.001	P=0.037	P=0.065
Last observation carried forward method of imputation*	P=0.0016	P=0.074	P=0.17
Observed data only; converting visual acuity change scores to normalized ranks (van der Waerden scores)*	P<0.001	P=0.037	P=0.037
Observed data only; Wilcoxon rank sum test	P=0.0030	P=0.12	P=0.13
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME prior to 1 year visit*†	P<0.001	P=0.016	P=0.087
Observed data only; per-protocol analysis excluding any eye receiving any alternative treatment for DME prior to the 1 year visit or for which an injection deviation occurred (injection was deferred when required or injection was performed when it should have been deferred, based on protocol OCT and visual acuity criteria)*‡	P<0.001	P=0.034	P=0.090

DME = Diabetic macular edema

*Treatment group comparisons of mean change from ANCOVA model adjusting for continuous baseline visual acuity.

†Two in the aflibercept group, 4 in the bevacizumab group, and 1 in the ranibizumab group.

‡Fifteen in the aflibercept group, 20 in the bevacizumab group, and 17 in the ranibizumab group.

Table S4. Visual Acuity Outcomes Overall						
	Observed Data			Treatment Group Comparisons Differences in Mean Change or Difference in Proportions Adjusted 95% CI and Adjusted P Value		
(Letter Score)	**Aflibercept (N = 208)**	**Bevacizumab (N = 206)**	**Ranibizumab (N = 206)**	**Aflibercept vs Bevacizumab**	**Aflibercept vs Ranibizumab**	**Ranibizumab vs Bevacizumab**
Baseline						
Mean ± SD	65.0 ± 11.8	64.8 ± 11.2	65.1 ± 11.1			
~ Snellen equivalent	20/50	20/50	20/50			
1 Year						
Mean ± SD	78.4 ± 10.1	74.2 ± 13.2	76.3 ± 11.1			
~ Snellen equivalent	20/32	20/32	20/32			
Change from baseline (letter score)						
Mean ± SD	+13.3 ± 11.1	+9.7 ± 10.1	+11.2 ± 9.4	+3.5 (+1.4 to +5.7) P<0.001	+2.1 (+0.1 to +4.2) P=0.034	+1.4 (-0.4 to +3.2) P=0.12
≥ 10 letter improvement	132 (63%)	108 (52%)	122 (59%)	+13% (+1% to +24%) P=0.021	+4% (-3% to +12%) P=0.25	+8% (-2% to +19%) P=0.15
≥ 10 letters worsening	5 (2%)	6 (3%)	3 (1%)	0 (-3% to +3%) P=0.83	+1% (-2% to +4%) P=0.83	-1% (-4% to +2%) P=0.83
≥ 15 letter improvement	87 (42%)	59 (29%)	66 (32%)	+11% (+1% to +21%) P=0.028	+8% (0% to +17%) P=0.068	+3% (-5% to +11%) P=0.51
≥ 15 letters worsening	3 (1%)	3 (1%)	3 (1%)	0% (-2% to +2%) P=0.98	0% (-2% to +2%) P=0.98	0% (-2% to +2%) P=0.98

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 $(1-\alpha/i)*100\%$ 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 = <0.001
- P-value for interaction, treating baseline visual acuity as categorical (<69 versus $\geq$69) = 0.0016

Visual acuity change truncated to +/- 3SD (-22 and +44) to minimize the effects of outliers for 6 eyes in the aflibercept group (4 on the positive end, 2 on the negative end) and 2 eyes in the bevacizumab group (both on the negative end).

One-year visit data unavailable for 16 eyes in the aflibercept group, 12 eyes in the bevacizumab group, and 12 eyes 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 1 year change in visual acuity for the treatment group comparisons (including tests for interaction).

Table S5. 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 = 205)	**Bevacizumab (N = 203)**	**Ranibizumab (N = 201)**	**Aflibercept vs Bevacizumab**	**Aflibercept vs Ranibizumab**	**Ranibizumab vs Bevacizumab**
Baseline CSF (µm) mean ± SD	412 ± 133	414 ± 136	407 ± 122			
CSF 1 year (µm) mean ± SD	240 ± 70	311 ± 124	257 ± 88			
CSF change from baseline (µm)						
Mean ± SD	-169 ± 138	-101 ± 121	-147 ± 134	-69.9 (-91.1,-48.6) P<0.001	-18.6 (-36.0,-1.2) P=0.036	-51.2 (-71.2,-31.3) P<0.001
CSF <250 µm	135 (66%)	74 (36%)	116 (58%)	+31% (+20%, +42%) P<0.001	+7% (-2%, +17%) P=0.13	+24% (+13%, +35%) P<0.001

SD = standard deviation; CSF= central subfield thickness

All baseline and 1-year optical coherence tomography (OCT) scans were graded by Duke Reading Center. In addition, a random sample of OCT images from other visits and images for which the investigator believed central grading was needed also were graded by Duke Reading Center.

In addition to participants missing the 1-year visit, 3 in the aflibercept group, 3 in the bevacizumab group, and 5 in the ranibizumab group had 1-year visits but unusable OCT data to compute change due to the scan being missing or ungradable at either baseline or 1 year.

Baseline CSF values were converted from the thickness value measured on a Spectralis or Cirrus OCT machine to a Stratus equivalent value for 583 scans. One-year CSF values were converted from a thickness value measured on a Spectralis or Cirrus OCT machine to a Stratus equivalent value for 604 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 26 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 visual acuity 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.

Table S6. Baseline Characteristics			
	Aflibercept (N = 224)	**Bevacizumab (N = 218)**	**Ranibizumab (N = 218)**
Participant Characteristics			
Gender: Women - N (%)	110 (49%)	103 (47%)	94 (43%)
Age (yrs) - Median (25th, 75th percentile)	61 (54, 66)	63 (56, 68)	59 (53, 67)
Mean (Standard Deviation)	60 (10)	62 (10)	60 (11)
Race/Ethnicity - N (%)			
White	145 (65%)	139 (64%)	146 (67%)
Black/African-American	32 (14%)	37 (17%)	36 (17%)
Hispanic	37 (17%)	36 (17%)	30 (14%)
Asian	2 (<1%)	2 (<1%)	4 (2%)
Native Hawaiian/other Pacific Islander	2 (<1%)	2 (<1%)	0
American Indian/Alaskan Native	1 (<1%)	0	0
More than one race	4 (2%)	1 (<1%)	1 (<1%)
Unknown/not reported	1 (<1%)	1 (<1%)	1 (<1%)
Diabetes Type - N (%)			
Type 1	22 (10%)	12 (6%)	16 (7%)
Type 2	196 (88%)	205 (94%)	196 (90%)
Uncertain	6 (3%)	1 (<1%)	6 (3%)
Duration of Diabetes (yrs) - Median (25th, 75th percentile)	15 (8, 21)	17 (11, 24)	16 (11, 23)
Hemoglobin A1c (%) - Median (25th, 75th percentile)*	7.6 (6.8, 9.1)	7.7 (6.8, 8.8)	7.8 (6.9, 9.2)
Prior Myocardial Infarction - N (%)	13 (6%)	14 (6%)	16 (7%)
Prior Coronary Artery Disease (without myocardial infarction) - N (%)	22 (10%)	27 (12%)	34 (16%)

Prior Stroke - N (%)	8 (4%)	13 (6%)	10 (5%)
Prior Transient Ischemic Attacks - N (%)	6 (3%)	8 (4%)	10 (5%)
Prior Gastrointestinal Perforation - N (%)	0	2 (<1%)	0
Prior Renal Disease - N (%)	20 (9%)	26 (12%)	26 (12%)
Prior Hypertension - N (%)	177 (79%)	181 (83%)	175 (80%)
Prior Severe Hemorrhage[†] - N (%)	3 (1%)	3 (1%)	0
Mean Arterial Blood Pressure[‡] **(mmHg)** - Median (25^{th}, 75^{th} percentile)	101 (91, 112)	101 (91, 109)	102 (94, 112)
Albumin/Creatinine Ratio (mg/g)[§] - Median (25^{th}, 75^{th} percentile)	69 (14, 548)	68 (16, 660)	61 (13, 777)
Smoke cigarettes on a daily basis - N (%)			
Never	143 (64%)	132 (61%)	145 (67%)
Prior	66 (29%)	73 (33%)	53 (24%)
Current	15 (7%)	13 (6%)	20 (9%)
Body Mass Index[‖] **(kg/m^2)** - Median (25^{th}, 75^{th} percentile)	31.8 (27.4, 37.3)	32.9 (28.7, 37.6)	32.3 (28.2, 37.2)
Ocular Characteristics			
Visual Acuity			
Letter Score - Median (75^{th}, 25^{th} percentile)	69 (74, 59)	69 (72, 60)	68 (73, 58)
~ Snellen Equivalent - Median (75^{th}, 25^{th} percentile)	20/40 (20/32, 20/63)	20/40 (20/40, 20/63)	20/50 (20/40, 20/80)
20/50 or Worse (Letter Score <69) - N (%)	112 (50%)	107 (49%)	110 (50%)
20/32-20/40 (Letter Score 78- 69) - N (%)	112 (50%)	111 (51%)	108 (50%)

OCT Central Subfield (µm)[¶] - Median (25th, 75th percentile)	387 (310, 483)	376 (305, 477)	390 (310, 493)
OCT Retinal Volume (mm^3)[††] - Median (25th, 75th percentile)	8.5 (7.7, 10.2)	8.4 (7.4, 10.0)	8.8 (7.7, 9.8)
Lens Status (clinical exam) - N (%)			
Phakic	166 (74%)	160 (73%)	173 (79%)
Pseudophakic	58 (26%)	58 (27%)	45 (21%)
Diabetic Retinopathy Severity[‡‡] (ETDRS level)			
Absent or minimal NPDR (level 10-20)	7 (3%)	6 (3%)	5 (2%)
Mild to moderately severe NPDR (level 35, 43, 47)	150 (68%)	131 (62%)	145 (67%)
Severe NPDR (level 53)	17 (8%)	15 (7%)	18 (8%)
Prior PRP; without current PDR (level 60)	17 (8%)	21 (10%)	16 (7%)
Mild to moderate PDR (level 61 and 65)	28 (13%)	31 (15%)	23 (11%)
High risk PDR (level 71 and 75)	2 (1%)	7 (3%)	9 (4%)
Prior Focal/Grid Laser for DME - N (%)	80 (36%)	84 (39%)	80 (37%)
Prior Anti-VEGF for DME - N (%)	24 (11%)	31 (14%)	29 (13%)
Prior Other Treatment for DME** - N (%)	14 (6%)	12 (6%)	11 (5%)
Prior PRP - N (%)	32 (14%)	40 (18%)	35 (16%)
Intraocular Pressure (mmHg) - Median (25th, 75th percentile)	15 (13, 18)	15 (14, 18)	16 (14, 18)

OCT = optical coherence tomography, ETDRS = early treatment diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, PRP = panretinal photocoagulation, PDR = proliferative diabetic retinopathy, DME = diabetic macular edema

*****Missing Hemoglobin A1c data: aflibercept (5) and ranibizumab (1).

†Severe hemorrhage includes hemoptysis, epistaxis, gastrointestinal bleeding, or vaginal bleeding.

‡Each participant value was a result of 3 sets of measurements yielding 3 mean arterial blood pressure values [diastolic + 1/3(systolic-diastolic)] averaged together for a single participant value.

§Missing Albumin/Creatinine data: aflibercept (3), bevacizumab (1), ranibizumab (2).

‖Missing body mass index data: aflibercept (17), bevacizumab (22), and ranibizumab (23).

¶Missing OCT central subfield thickness measurements: aflibercept (3), bevacizumab (2), ranibizumab (3).

†† Missing OCT retinal volume measurements: aflibercept (40), bevacizumab (35), and ranibizumab (36).

‡‡ Missing diabetic retinopathy severity: aflibercept (3), bevacizumab (7), and ranibizumab (2).

****** Includes prior treatment with intravitreous corticosteroid, peribulbar corticosteroid or vitrectomy.

Table S7. Treatment for Diabetic Macular Edema Prior to the 1 Year Visit				
	Aflibercept (N = 208)	**Bevacizumab (N = 206)**	**Ranibizumab (N = 206*)**	**P-Value**
Intravitreous Injection				
Total Number of Injections Prior to 1 Year[†] (Maximum = 13) - N (%)				
0-2	0	0	0	
3	0	1 (<1%)	0	
4	3 (1%)	2 (1%)	3 (1%)	
5	4 (2%)	3 (1%)	3 (1%)	
6	17 (8%)	19 (9%)	16 (8%)	
7	23 (11%)	21 (10%)	21 (10%)	
8	24 (12%)	16 (8%)	26 (13%)	
9	45 (22%)	27 (13%)	27 (13%)	
10	27 (13%)	31 (15%)	37 (18%)	
11	40 (19%)	31 (15%)	34 (17%)	
12	17 (8%)	33(16%)	29 (14%)	
13	8 (4%)	22 (11%)	10 (5%)	
Mean (Standard Deviation)	9.2 (2.0)	9.7 (2.3)	9.4 (2.1)	
Median (25^{th}, 75^{th} percentile)	9 (8, 11)	10 (8, 12)	10 (8, 11)	0.045[‡]
All visits, prior to 1 year - N (%)	**N = 2693**	**N = 2631**	**N = 2607**	
Visits with injections received	1991 (74%)	2055 (78%)	2011 (77%)	
Visits with injections deferred due to;				
success	63 (2%)	15 (1%)	63 (2%)	
stability	606 (23%)	527 (20%)	509 (20%)	
failure	2 (<1%)	5 (<1%)	0	
other reasons	31 (1%)	29 (1%)	24 (1%)	
Follow-up Visits Requiring Re-Injection Per Protocol based on OCT and visual acuity criteria - N	**N = 1780**	**N = 1854**	**N = 1805**	
Injection Not Given - N (%)	15 (1%)	21 (1%)	16 (1%)	
Reasons				
Adverse event precluding treatment	6	9	9	
Subject refused	1	4	2	
Treatment not needed per investigator	6	3	3	
Other	2	5	2	
Injection Received when Protocol Indicated Deferral	1	4	4	

Laser Photocoagulation				
Total Number of Focal/Grid Laser Treatments Prior to 24 Weeks	0	0	0	
Total Number of Laser Treatments Between 24 weeks and 1 Year[†] - N (%)				
0	132 (63%)	91 (44%)	111 (54%)	<0.001[§]
1	57 (27%)	85 (41%)	77 (37%)	
2	19 (9%)	30 (15%)	18 (9%)	
Eyes for which focal/grid laser was indicated per visual acuity or OCT protocol criteria at 1 or more visit but not performed prior to 1 year - N (%)	15 (7%)	17 (8%)	10 (5%)	
Other				
Eyes receiving 1 or more alternative treatments for DME other than laser - N (%)/ Number of those eyes meeting failure criteria	2 (1%)/ (1)	4 (2%)/ (2)	1 (<1%)/ (0)	

OCT = optical coherence tomography, DME = diabetic macular edema

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

†Only includes participants that completed the 1 year visit.

‡Global (overall 3 group comparison) P-value from Kruskal-Wallis Test. Pairwise comparisons from Wilcoxon Rank Sum Test (adjusted for multiple comparisons by taking the maximum of the global and pairwise comparison P-values): aflibercept-bevacizumab: P=0.045, aflibercept-ranibizumab: P=0.19, bevacizumab-ranibizumab: P=0.22.

§Global (overall 3 group comparison) P-value from Fisher's Exact Test for proportion with no laser versus any laser prior to 1 year. 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=0.058, bevacizumab-ranibizumab: P=0.061.

Table S8. Change in Visual Acuity Letter Score from Baseline to 1 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							0.012 (0.0049)
< 400 µm	112	+10.9 ± 10.1	112	+9.5 ± 7.6	109	+10.1 ± 9.5	
≥ 400 µm	93	+16.2 ± 11.7	91	+9.6 ± 11.7	93	+12.4 ± 9.0	
Any Prior Anti-VEGF Treatment							0.39
No	185	+13.7 ± 11.2	174	+9.7 ± 10.5	178	+11.9 ± 9.4	
Yes	23	+10.3 ± 10.5	32	+9.3 ± 8.2	28	+7.0 ± 8.1	
Lens Status							0.90
Pseudophakic	53	+11.6 ± 11.1	57	+8.1 ± 11.2	43	+9.7 ± 9.0	
Phakic	155	+13.9 ± 11.1	149	+10.3 ± 9.6	163	+11.6 ± 9.4	

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 1 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 S9. Change in Retinal Volume from Baseline to 1 Year

Overall

	Aflibercept (N = 162)	Bevacizumab (N = 153)	Ranibizumab (N = 162)
Baseline Volume - Mean ± SD	8.9 ± 1.9	8.8 ± 1.8	8.9 ± 1.7
Volume at 1 Year - Mean ± SD	7.2 ± 0.9	7.8 ± 1.4	7.3 ± 1.0
Change in Volume from Baseline - Mean ± SD	-1.7 ± 1.6	-1.0 ± 1.2	-1.7 ± 1.5

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

	Aflibercept (N = 79)	Bevacizumab (N = 72)	Ranibizumab (N = 72)
Baseline Volume - Mean ± SD	9.6±2.1	9.3±2.0	9.2±1.9
Volume at 1 Year - Mean ± SD	7.3±1.0	8.0±1.6	7.2±1.2
Change in Volume from Baseline - Mean ± SD	-2.3±1.8	-1.3±1.4	-2.1±1.8

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

	Aflibercept (N = 83)	Bevacizumab (N = 81)	Ranibizumab (N = 90)
Baseline Volume - Mean ± SD	8.4±1.3	8.4 ±1.5	8.7±1.4
Volume at 1 Year - Mean ± SD	7.2±0.7	7.6±1.1	7.4±0.9
Change in Volume from Baseline - Mean ± SD	-1.2±1.0	-0.8±0.9	-1.3±1.2

- All baseline and 1-year optical coherence tomography (OCT) scans were graded by Duke Reading Center. In addition a random sample of OCT images from other visits and images for which the investigator believed central grading was needed also were graded by Duke Reading Center.
- In addition to participants missing the 1-year visit, 46 in the aflibercept group, 53 in the bevacizumab group, and 44 in the ranibizumab group had 1-year visits but unusable OCT data to compute change due to the scan being missing or ungradable at either baseline or 1 year.
- Baseline volume values were converted from the thickness value measured on a Spectralis or Cirrus OCT machine to a Stratus equivalent value for 459 scans. One-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 17 eyes.

Table S10. Systemic Adverse Events through 1 Year: Stratified by Whether Bilateral Study Drug was Received Prior to 1 Year

Participants with Unilateral Study Anti-VEGF Treatment prior to 1 year *

	Aflibercept (N = 95)	Bevacizumab (N = 96)	Ranibizumab (N = 97)
Vascular Events According to the Antiplatelet Trialists' Collaboration[5] occurring at least once through 1 year[†] (No. Participants)			
Non-fatal myocardial infarction	3 (3%)	0	2 (2%)
Non-fatal stroke	0	2 (2%)	2 (2%)
Vascular death (from any potential vascular or unknown cause)	0	4 (4%)	1 (1%)
Any Antiplatlet Trialists` Collaboration Event	3 (3%)	6 (6%)	5 (5%)
Pre-specified Systemic Events occurring at least once through 1 year[†] (No. Participants)			
Death (any cause)	0	5 (5%)	2 (2%)
Hospitalization	20 (21%)	12 (13%)	23 (24%)
Serious adverse event	24 (25%)	16 (17%)	25 (26%)
Gastrointestinal[‡]	17 (18%)	11 (11%)	18 (19%)
Kidney[§]	9 (9%)	4 (4%)	4 (4%)
Hypertension	7 (7%)	3 (3%)	8 (8%)

Participants with Bilateral Study Anti-VEGF Treatment prior to 1 year *

	Aflibercept (N = 129)	Bevacizumab (N = 122)	Ranibizumab (N = 121)
Vascular Events According to the Antiplatelet Trialists' Collaboration[5] occurring at least once through 1 year[†] (No. Participants)			
Non-fatal myocardial infarction	1 (<1%)	1 (<1%)	1 (<1%)
Non-fatal stroke	0	2 (2%)	2 (2%)
Vascular death (from any potential vascular or unknown cause)	2 (2%)	0	2 (2%)
Any Antiplatlet Trialists` Collaboration Event	3 (2%)	3 (2%)	5 (4%)
Pre-specified Systemic Events occurring at least once through 1 year[†] (No. Participants)			
Death (any cause)	3 (2%)	0	2 (2%)
Hospitalization	29 (22%)	28 (23%)	26 (21%)
Serious adverse event	35 (27%)	30 (25%)	30 (25%)
Gastrointestinal[‡]	27 (21%)	29 (24%)	20 (17%)
Kidney[§]	19 (15%)	19 (16%)	20 (17%)
Hypertension	19 (15%)	13 (11%)	18 (15%)

*One-year visit (if the 1 year visit was not completed, then 365 days was used).

†One-year visit (if the 1 year visit was not completed or if it was completed prior to 365 days, then 365 days was used).

‡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 S11. Post Hoc Analysis: Events by Medical Dictionary for Regulatory Activities System Organ Class Through 1 Year

	Aflibercept (N = 224)	Bevacizumab (N = 218)	Ranibizumab (N = 218)	P Value*
Number of Participants with an Event in the Given System Organ Class Through 1 year†				
Blood and lymphatic system disorders	14 (6%)	5 (2%)	8 (4%)	0.12
Cardiac disorders	14 (6%)	11 (5%)	23 (11%)	0.081
Ear and labyrinth disorders	6 (3%)	4 (2%)	1 (<1%)	0.20
Endocrine disorders	28 (13%)	22 (10%)	25 (11%)	0.73
Eye disorders	134 (60%)	141 (65%)	140 (64%)	0.52
Gastrointestinal disorders	44 (20%)	40 (18%)	38 (17%)	0.84
General disorders and administration site conditions	29 (13%)	26 (12%)	24 (11%)	0.82
Hepatobiliary disorders	1 (<1%)	3 (1%)	3 (1%)	0.58
Immune system disorders	12 (5%)	11 (5%)	10 (5%)	0.97
Infections and infestations	25 (11%)	26 (12%)	26 (12%)	0.96
Injury, poisoning and procedural complications	18 (8%)	19 (9%)	19 (9%)	0.95
Investigations	22 (10%)	12 (6%)	19 (9%)	0.22
Metabolism and nutrition disorders	29 (13%)	17 (8%)	23 (11%)	0.21
Musculoskeletal and connective tissue disorders	55 (25%)	57 (26%)	53 (24%)	0.91
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (<1%)	4 (2%)	2 (<1%)	0.32
Nervous system disorders	43 (19%)	43 (20%)	50 (23%)	0.58
Psychiatric disorders	12 (5%)	12 (6%)	14 (6%)	0.91
Renal and urinary disorders	41 (18%)	36 (17%)	32 (15%)	0.60
Reproductive system and breast disorders	3 (1%)	3 (1%)	5 (2%)	0.75
Respiratory, thoracic and mediastinal disorders	72 (32%)	60 (28%)	68 (31%)	0.53
Skin and subcutaneous tissue disorders	37 (17%)	29 (13%)	27 (12%)	0.43
Social circumstances	0	1 (<1%)	0	0.66
Surgical and medical procedures	12 (5%)	10 (5%)	10 (5%)	0.92
Vascular disorders	32 (14%)	25 (11%)	40 (18%)	0.13

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

†One-year visit (If the 1 year visit was not completed or if it was completed prior to 365 days, then 365 days was used.)

Table S12. Post Hoc Analysis: Cardiovascular Events through 1 Year

Overall

Events occurring at least once through 1 year* (No. Participants)	Aflibercept (N = 224)	Bevacizumab (N = 218)	Ranibizumab (N = 218)	P Value
Any Cardiovascular Event,† excluding Hypertension	20 (9%)	19 (9%)	37 (17%)	0.012‡
Any Cardiovascular Event†	42 (19%)	35 (16%)	56 (26%)	0.038§
Cardiac Events	14 (6%)	12 (6%)	23 (11%)	
Cerebrovascular Events	0	4 (2%)	10 (5%)	
Peripheral Vascular Disease Events	1 (<1%)	2 (<1%)	2 (<1%)	
Venous Disease Events	1 (<1%)	2 (<1%)	2 (<1%)	
Hypertension Events	26 (12%)	16 (7%)	26 (12%)	
Other Cardiovascular Events	6 (3%)	2 (<1%)	4 (2%)	

Participants with Unilateral Study Anti-VEGF Treatment prior to 1 year‖

Events occurring at least once through 1 year* (No. Participants)	Aflibercept (N = 95)	Bevacizumab (N = 96)	Ranibizumab (N = 97)
Any Cardiovascular Event,† excluding Hypertension	8 (8%)	9 (9%)	16 (16%)
Any Cardiovascular Event†	15 (16%)	12 (13%)	22 (23%)
Cardiac Events	5 (5%)	5 (5%)	9 (9%)
Cerebrovascular Events	0	2 (2%)	5 (5%)
Peripheral Vascular Disease Events	1 (1%)	0	2 (2%)
Venous Disease Events	1 (1%)	1 (1%)	0
Hypertension Events	7 (7%)	3 (3%)	8 (8%)
Other Cardiovascular Events	2 (2%)	1 (1%)	1 (1%)

Participants with Bilateral Study Anti-VEGF Treatment prior to 1 year‖

Events occurring at least once through 1 year* (No. Participants)	Aflibercept (N = 129)	Bevacizumab (N = 122)	Ranibizumab (N = 121)
Any Cardiovascular Event,† excluding Hypertension	12 (9%)	10 (8%)	21 (17%)

Any Cardiovascular Event †	27 (21%)	23 (19%)	34 (28%)
Cardiac Events	9 (7%)	7 (6%)	14 (12%)
Cerebrovascular Events	0	2 (2%)	5 (4%)
Peripheral Vascular Disease Events	0	2 (2%)	0
Venous Disease Events	0	1 (<1%)	2 (2%)
Hypertension Events	19 (15%)	13 (11%)	18 (15%)
Other Cardiovascular Events	4 (3%)	1 (<1%)	3 (2%)

Anti-VEGF = anti vascular endothelial growth factor

***** One-year visit (If the 1 year visit was not completed or if it was completed prior to 365 days, then 365 days was used).

† 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, and stent placement. Participants with multiple events are only included once in the overall tabulation but could be included in more than one of the subcategories.

‡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=1.0, aflibercept-ranibizumab: P=0.015, bevacizumab-ranibizumab: P=0.014. 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=0.024. Pairwise comparisons from this model (adjusted for multiple comparisons by taking the maximum of the global and pairwise comparison P-values): bevacizumab-aflibercept: P=0.68, ranibizumab-aflibercept: P=0.040, ranibizumab-bevacizumab: P=0.024.

§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=0.53, aflibercept-ranibizumab: P=0.087, bevacizumab-ranibizumab: P=0.038. 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=0.081. Pairwise comparisons from this model (adjusted for multiple comparisons by taking the maximum of the global and pairwise comparison P-values): bevacizumab-aflibercept: P=0.37, ranibizumab-aflibercept: P=0.19, ranibizumab-bevacizumab: P=0.081.

‖One-year visit (If the 1 year visit was not completed, then 365 days was used).

Table S13. All Ocular Adverse Events Occurring in the Study Eye through 1 Year *†			
No. Events (No. Participants)	**Aflibercept (N = 224)**	**Bevacizumab (N = 218)**	**Ranibizumab (N = 218)**
Anterior chamber			
Anterior chamber cell	0 (0)	1 (1)	2 (1)
Anterior chamber opacity	1 (1)	0 (0)	0 (0)
Foreign body in anterior chamber	0 (0)	1 (1)	0 (0)
Post procedural complication	0 (0)	1 (1)	0 (0)
Conjunctiva			
Conjunctival haemorrhage	43 (25)	56 (36)	40 (23)
Conjunctival hyperaemia	0 (0)	1 (1)	2 (2)
Conjunctival oedema	2 (2)	0 (0)	0 (0)
Conjunctivitis	3 (3)	0 (0)	1 (1)
Conjunctivitis allergic	0 (0)	2 (2)	0 (0)
Conjunctivitis viral	0 (0)	0 (0)	1 (1)
Eye discharge	1 (1)	2 (2)	1 (1)
Ocular hyperaemia	0 (0)	7 (7)	9 (9)
Pinguecula	0 (0)	0 (0)	1 (1)
Cornea			
Corneal abrasion	4 (3)	7 (7)	5 (5)
Corneal disorder	0 (0)	0 (0)	4 (3)
Corneal oedema	1 (1)	0 (0)	0 (0)
Corneal opacity	1 (1)	0 (0)	0 (0)
Corneal pigmentation	2 (2)	0 (0)	0 (0)
Keratitis	0 (0)	1 (1)	0 (0)
Keratitis sicca	1 (1)	0 (0)	0 (0)
Keratopathy	1 (1)	0 (0)	0 (0)
Punctate keratitis	4 (3)	2 (2)	4 (4)
External			
Arthropod bite	0 (0)	0 (0)	1 (1)
Dry eye	13 (13)	8 (8)	9 (9)
Dry eye syndrome	1 (1)	1 (1)	2 (2)
Eye infection	1 (1)	0 (0)	0 (0)
Eye irritation	21 (12)	19 (14)	15 (12)
Eye swelling	0 (0)	2 (2)	2 (2)
Hypersensitivity	1 (1)	0 (0)	0 (0)
Lacrimation increased	11 (11)	5 (5)	8 (8)
Ocular discomfort	5 (3)	2 (2)	5 (4)
Periorbital contusion	0 (0)	1 (1)	0 (0)

Glaucoma-IOP			
Glaucoma	0 (0)	1 (1)	2 (1)
Intraocular pressure increased	4 (4)	2 (2)	7 (5)
Ocular hypertension	1 (1)	2 (2)	1 (1)
Inflammation			
Choroiditis	0 (0)	1 (1)	0 (0)
Episcleritis	0 (0)	0 (0)	1 (1)
Iritis	4 (2)	0 (0)	1 (1)
Lens			
Cataract	10 (10)	9 (9)	8 (8)
Cataract cortical	0 (0)	2 (2)	1 (1)
Cataract nuclear	1 (1)	1 (1)	2 (2)
Cataract operation	1 (1)	0 (0)	2 (2)
Cataract operation complication	0 (0)	1 (1)	0 (0)
Cataract subcapsular	4 (4)	4 (4)	4 (4)
Posterior capsule opacification	4 (4)	3 (3)	4 (3)
Lids			
Blepharal papilloma	1 (1)	0 (0)	1 (1)
Blepharitis	3 (2)	0 (0)	4 (4)
Blepharospasm	1 (1)	1 (1)	2 (2)
Cutis laxa	1 (1)	1 (1)	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)	0 (0)	0 (0)
Eyelid ptosis	1 (1)	0 (0)	1 (1)
Hordeolum	2 (2)	0 (0)	2 (2)
Trichiasis	0 (0)	1 (1)	0 (0)
Miscellaneous-eye			
Asthenopia	1 (1)	0 (0)	1 (1)
Optic nerve			
Optic disc disorder	1 (1)	0 (0)	1 (1)
Optic nerve cupping	1 (1)	0 (0)	0 (0)
Retina			
Cystoid macular oedema	0 (0)	1 (1)	0 (0)
Diabetic retinal oedema	1 (1)	2 (2)	1 (1)
Diabetic retinopathy	0 (0)	4 (3)	0 (0)
Macular fibrosis	4 (4)	5 (5)	0 (0)
Macular hole	0 (0)	1 (1)	0 (0)

Macular ischaemia	2 (2)	1 (1)	1 (1)
Retinal aneurysm	0 (0)	0 (0)	1 (1)
Retinal artery embolism	1 (1)	1 (1)	2 (2)
Retinal degeneration	0 (0)	0 (0)	1 (1)
Retinal disorder	0 (0)	1 (1)	0 (0)
Retinal exudates	5 (5)	5 (5)	5 (4)
Retinal haemorrhage	2 (2)	6 (5)	3 (3)
Retinal ischaemia	0 (0)	2 (2)	1 (1)
Retinal neovascularisation	2 (2)	1 (1)	2 (1)
Retinal tear	0 (0)	1 (1)	1 (1)
Retinal vascular disorder	0 (0)	0 (0)	1 (1)
Retinal vein occlusion	0 (0)	1 (1)	0 (0)
Retinopathy	1 (1)	0 (0)	0 (0)
Vitreous adhesions	2 (2)	1 (1)	0 (0)
Sensation-pain			
Abnormal sensation in eye	0 (0)	1 (1)	1 (1)
Eye pain	28 (21)	30 (23)	16 (16)
Eye pruritus	8 (8)	9 (8)	9 (8)
Eyelid pain	1 (1)	3 (3)	0 (0)
Facial pain	1 (1)	0 (0)	0 (0)
Foreign body sensation in eyes	3 (3)	6 (6)	6 (5)
Headache	0 (0)	1 (1)	1 (1)
Pain	0 (0)	1 (1)	0 (0)
Strabismus			
Strabismus	0 (0)	1 (1)	0 (0)
Visual field			
Scotoma	0 (0)	2 (2)	0 (0)
Visual symptoms/abnormality			
Altered visual depth perception	0 (0)	1 (1)	0 (0)
Diplopia	5 (5)	1 (1)	7 (7)
Glare	0 (0)	1 (1)	2 (2)
Metamorphopsia	1 (1)	4 (4)	2 (2)
Migraine with aura	1 (1)	0 (0)	1 (1)
Night blindness	0 (0)	1 (1)	0 (0)
Photophobia	6 (6)	5 (5)	3 (3)
Photopsia	4 (4)	3 (3)	8 (6)
Reading disorder	0 (0)	1 (1)	0 (0)
Vision blurred	30 (27)	35 (33)	49 (39)
Visual acuity reduced	13 (12)	16 (15)	14 (12)

Visual impairment	10 (9)	6 (6)	8 (6)
Vitreous			
Hyalosis asteroid	0 (0)	0 (0)	1 (1)
Vitreal cells	1 (1)	0 (0)	1 (1)
Vitreous degeneration	0 (0)	3 (2)	1 (1)
Vitreous detachment	7 (7)	8 (8)	4 (4)
Vitreous disorder	0 (0)	0 (0)	1 (1)
Vitreous floaters	34 (30)	45 (41)	41 (34)
Vitreous haemorrhage	6 (4)	13 (9)	7 (7)

*One year visit (If the 1 year visit was not completed, then 365 days was used).

†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 through 1 Year * †			
No. Events (No. Participants)	**Aflibercept (N = 129)**	**Bevacizumab (N = 122)**	**Ranibizumab (N = 121)**
Anterior chamber			
Anterior chamber cell	0 (0)	1 (1)	0 (0)
Conjunctiva			
Conjunctival haemorrhage	24 (11)	27 (13)	14 (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)	1 (1)	0 (0)
Pinguecula	0 (0)	0 (0)	1 (1)
Cornea			
Corneal abrasion	2 (2)	3 (2)	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 irritation	0 (0)	2 (2)	0 (0)
Corneal oedema	0 (0)	0 (0)	2 (1)
Corneal scar	1 (1)	0 (0)	0 (0)
Keratitis	0 (0)	1 (1)	0 (0)
Punctate keratitis	2 (2)	1 (1)	0 (0)
External			
Arthropod sting	1 (1)	0 (0)	0 (0)
Dry eye	5 (5)	6 (6)	3 (3)
Eye infection	1 (1)	0 (0)	0 (0)
Eye irritation	7 (3)	4 (4)	9 (7)
Eye swelling	0 (0)	1 (1)	0 (0)
Lacrimation increased	5 (5)	1 (1)	2 (2)
Ocular discomfort	3 (1)	1 (1)	4 (4)
Ophthalmic herpes simplex	0 (0)	2 (1)	0 (0)
Glaucoma-IOP			
Glaucoma	0 (0)	0 (0)	1 (1)
Hypotony of eye	1 (1)	0 (0)	0 (0)
Intraocular pressure increased	2 (2)	4 (3)	2 (2)
Ocular hypertension	1 (1)	0 (0)	1 (1)
Inflammation			
Anterior chamber flare	1 (1)	1 (1)	0 (0)
Iritis	1 (1)	1 (1)	0 (0)

Iris			
Iris adhesions	1 (1)	0 (0)	0 (0)
Lens			
Cataract	4 (4)	4 (4)	3 (3)
Cataract cortical	0 (0)	3 (3)	1 (1)
Cataract nuclear	1 (1)	0 (0)	0 (0)
Cataract operation	1 (1)	0 (0)	0 (0)
Cataract operation complication	0 (0)	0 (0)	1 (1)
Cataract subcapsular	2 (2)	1 (1)	2 (2)
Posterior capsule opacification	2 (2)	0 (0)	3 (2)
Lids			
Blepharitis	0 (0)	1 (1)	3 (3)
Chalazion	1 (1)	0 (0)	0 (0)
Cutis laxa	0 (0)	1 (1)	0 (0)
Eyelid margin crusting	1 (1)	1 (1)	0 (0)
Eyelid oedema	2 (2)	0 (0)	0 (0)
Hordeolum	2 (1)	0 (0)	0 (0)
Skin lesion	0 (0)	0 (0)	1 (1)
Optic nerve			
Optic atrophy	0 (0)	0 (0)	1 (1)
Optic nerve cupping	1 (1)	0 (0)	0 (0)
Papilloedema	1 (1)	0 (0)	0 (0)
Retina			
Cystoid macular oedema	0 (0)	0 (0)	2 (2)
Diabetic retinal oedema	6 (6)	6 (6)	4 (4)
Diabetic retinopathy	1 (1)	1 (1)	4 (4)
Eye naevus	0 (0)	0 (0)	1 (1)
Macular degeneration	0 (0)	0 (0)	1 (1)
Macular fibrosis	2 (2)	6 (6)	1 (1)
Macular hole	0 (0)	1 (1)	0 (0)
Macular oedema	1 (1)	0 (0)	2 (2)
Retinal aneurysm	0 (0)	1 (1)	0 (0)
Retinal exudates	1 (1)	6 (6)	2 (2)
Retinal haemorrhage	1 (1)	1 (1)	5 (5)
Retinal ischaemia	0 (0)	1 (1)	0 (0)
Retinal laser coagulation	1 (1)	0 (0)	1 (1)
Retinal neovascularisation	2 (2)	0 (0)	0 (0)
Retinal vein occlusion	0 (0)	1 (1)	0 (0)
Retinopathy	1 (1)	0 (0)	0 (0)
Vitreous adhesions	1 (1)	0 (0)	0 (0)
Sensation-pain			

Eye pain	13 (9)	14 (13)	7 (5)
Eye pruritus	3 (3)	1 (1)	8 (8)
Eyelid pain	0 (0)	1 (1)	0 (0)
Foreign body sensation in eyes	1 (1)	3 (3)	1 (1)
Headache	1 (1)	0 (0)	2 (2)
Pain	0 (0)	1 (1)	0 (0)
Visual symptoms/abnormality			
Altered visual depth perception	0 (0)	1 (1)	0 (0)
Diplopia	0 (0)	0 (0)	4 (4)
Metamorphopsia	0 (0)	2 (2)	2 (2)
Migraine with aura	1 (1)	0 (0)	0 (0)
Photophobia	5 (5)	1 (1)	1 (1)
Photopsia	3 (3)	3 (3)	5 (3)
Reading disorder	0 (0)	1 (1)	0 (0)
Vision blurred	16 (15)	11 (11)	22 (20)
Visual acuity reduced	7 (6)	6 (6)	7 (7)
Visual impairment	2 (2)	7 (5)	4 (3)
Vitreous			
Endophthalmitis	2 (1)	0 (0)	1 (1)
Vitreal cells	1 (1)	1 (1)	0 (0)
Vitreous degeneration	0 (0)	2 (1)	1 (1)
Vitreous detachment	7 (7)	4 (4)	1 (1)
Vitreous floaters	14 (13)	15 (14)	20 (14)
Vitreous haemorrhage	5 (5)	10 (8)	3 (3)

*One year visit (If the 1 year visit was not completed, then 365 days was used).

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

Table S15. All Systemic Adverse Events Occurring Through 1 Year*†			
No. Events (No. Participants)	Aflibercept (N = 224)	Bevacizumab (N = 218)	Ranibizumab (N = 218)
Blood and lymphatic system disorders			
Anaemia	9 (9)	2 (2)	7 (7)
Anaemia of chronic disease	2 (2)	2 (2)	1 (1)
Coagulopathy	0 (0)	1 (1)	0 (0)
Leukocytosis	1 (1)	0 (0)	0 (0)
Lymphadenopathy	1 (1)	0 (0)	0 (0)
Lymphangitis	1 (1)	0 (0)	0 (0)
Lymphoedema	1 (1)	0 (0)	0 (0)
Cardiac disorders			
Acute coronary syndrome	0 (0)	0 (0)	1 (1)
Angina pectoris	0 (0)	1 (1)	0 (0)
Arrhythmia	1 (1)	0 (0)	0 (0)
Arteriosclerosis coronary artery	0 (0)	0 (0)	1 (1)
Atrial fibrillation	2 (2)	0 (0)	2 (2)
Atrial flutter	0 (0)	0 (0)	1 (1)
Atrioventricular block second degree	0 (0)	0 (0)	2 (2)
Bradycardia	0 (0)	1 (1)	0 (0)
Cardiac arrest	1 (1)	1 (1)	0 (0)
Cardiac failure	0 (0)	1 (1)	2 (2)
Cardiac failure congestive	3 (3)	6 (4)	10 (7)
Cardiomegaly	1 (1)	1 (1)	0 (0)
Coronary artery disease	2 (2)	3 (3)	5 (5)
Diastolic dysfunction	2 (1)	1 (1)	0 (0)
Hypertensive heart disease	3 (2)	2 (2)	1 (1)
Myocardial infarction	4 (4)	1 (1)	4 (4)
Palpitations	0 (0)	0 (0)	2 (2)
Pericardial effusion	0 (0)	0 (0)	1 (1)
Tachycardia	2 (1)	1 (1)	0 (0)
Tricuspid valve incompetence	0 (0)	0 (0)	1 (1)
Ventricular hypokinesia	0 (0)	0 (0)	1 (1)
Ventricular tachycardia	0 (0)	0 (0)	1 (1)
Ear and labyrinth disorders			
Deafness	0 (0)	1 (1)	0 (0)
Ear infection	5 (5)	2 (2)	0 (0)
Ear pain	0 (0)	1 (1)	1 (1)
Tinnitus	1 (1)	0 (0)	0 (0)
Endocrine disorders			
Adrenal mass	0 (0)	1 (1)	0 (0)
Autoimmune thyroiditis	1 (1)	0 (0)	0 (0)

Diabetes mellitus	5 (4)	3 (3)	6 (5)
Diabetes mellitus inadequate control	11 (10)	7 (7)	11 (11)
Diabetic ketoacidosis	2 (2)	1 (1)	1 (1)
Glucocorticoid deficiency	1 (1)	0 (0)	0 (0)
Hyperglycaemia	3 (3)	2 (2)	0 (0)
Hyperthyroidism	0 (0)	0 (0)	1 (1)
Hypoglycaemia	9 (8)	8 (7)	6 (6)
Hypothyroidism	5 (5)	1 (1)	2 (2)
Gastrointestinal disorders			
Abdominal discomfort	4 (4)	6 (6)	0 (0)
Abdominal distension	0 (0)	0 (0)	1 (1)
Abdominal pain	3 (2)	6 (4)	3 (2)
Abdominal pain upper	1 (1)	2 (2)	2 (2)
Barrett's oesophagus	1 (1)	0 (0)	0 (0)
Clostridium difficile colitis	2 (2)	1 (1)	1 (1)
Colitis ulcerative	0 (0)	1 (1)	0 (0)
Colon cancer	0 (0)	1 (1)	1 (1)
Colorectal cancer	0 (0)	0 (0)	1 (1)
Constipation	5 (5)	5 (4)	7 (7)
Dental caries	1 (1)	0 (0)	0 (0)
Diabetic gastroparesis	2 (2)	0 (0)	1 (1)
Diarrhoea	6 (5)	12 (9)	9 (8)
Diverticulum	0 (0)	0 (0)	1 (1)
Dyspepsia	2 (2)	3 (3)	2 (2)
Gastric cancer stage I	0 (0)	0 (0)	1 (1)
Gastric ulcer	0 (0)	0 (0)	1 (1)
Gastritis	0 (0)	2 (2)	1 (1)
Gastroenteritis	0 (0)	2 (2)	1 (1)
Gastroenteritis viral	6 (6)	4 (4)	6 (5)
Gastrointestinal haemorrhage	0 (0)	0 (0)	1 (1)
Gastrointestinal stoma complication	0 (0)	0 (0)	1 (1)
Gastrooesophageal reflux disease	5 (5)	4 (4)	2 (2)
Haematochezia	1 (1)	0 (0)	0 (0)
Haemorrhoids	2 (2)	1 (1)	0 (0)
Hiatus hernia	0 (0)	0 (0)	1 (1)
Impaired gastric emptying	0 (0)	0 (0)	3 (1)
Intestinal perforation	0 (0)	1 (1)	0 (0)
Nausea	7 (7)	10 (7)	8 (7)
Oesophagitis	1 (1)	0 (0)	1 (1)
Pancreatitis	1 (1)	1 (1)	0 (0)
Peptic ulcer	0 (0)	1 (1)	1 (1)
Rectal haemorrhage	1 (1)	0 (0)	0 (0)
Rectal ulcer	0 (0)	0 (0)	1 (1)

Tooth abscess	3 (3)	1 (1)	4 (4)
Tooth fracture	2 (2)	1 (1)	0 (0)
Tooth impacted	0 (0)	1 (1)	0 (0)
Tooth infection	1 (1)	0 (0)	2 (2)
Toothache	1 (1)	1 (1)	0 (0)
Vomiting	14 (11)	10 (7)	4 (4)
General disorders and administration site conditions			
Chest discomfort	0 (0)	0 (0)	2 (2)
Chest pain	4 (4)	4 (3)	4 (4)
Chills	1 (1)	0 (0)	2 (2)
Cyst	2 (2)	2 (2)	2 (2)
Death	1 (1)	1 (1)	0 (0)
Device related infection	0 (0)	1 (1)	0 (0)
Facial pain	0 (0)	2 (2)	0 (0)
Fatigue	7 (7)	7 (7)	1 (1)
Generalised oedema	0 (0)	0 (0)	1 (1)
Lethargy	0 (0)	2 (2)	0 (0)
Local swelling	1 (1)	0 (0)	1 (1)
Necrosis	0 (0)	0 (0)	1 (1)
Oedema peripheral	5 (5)	5 (5)	8 (7)
Pain	5 (4)	1 (1)	4 (4)
Pyrexia	1 (1)	5 (5)	3 (2)
Swelling	4 (4)	2 (2)	2 (2)
Hepatobiliary disorders			
Cholecystitis acute	0 (0)	1 (1)	3 (3)
Cholecystitis chronic	0 (0)	1 (1)	0 (0)
Cholelithiasis	1 (1)	1 (1)	0 (0)
Immune system disorders			
Drug hypersensitivity	1 (1)	0 (0)	1 (1)
Hypersensitivity	2 (2)	2 (2)	1 (1)
Seasonal allergy	8 (8)	8 (8)	7 (7)
Urticaria	0 (0)	1 (1)	1 (1)
Infections and infestations			
Abscess	4 (4)	1 (1)	0 (0)
Bacteraemia	0 (0)	0 (0)	1 (1)
Diverticulitis	1 (1)	0 (0)	0 (0)
Escherichia infection	0 (0)	0 (0)	1 (1)
Fungal infection	1 (1)	0 (0)	0 (0)
Helicobacter infection	0 (0)	1 (1)	0 (0)
Infection	3 (3)	6 (6)	7 (7)
Influenza	11 (11)	8 (8)	13 (12)
Localized infection	5 (4)	9 (9)	7 (7)

Oral herpes	1 (1)	0 (0)	0 (0)
Postoperative wound infection	1 (1)	0 (0)	0 (0)
Sepsis	3 (3)	1 (1)	1 (1)
Septic shock	0 (0)	1 (1)	0 (0)
Staphylococcal infection	0 (0)	0 (0)	1 (1)
Injury, poisoning and procedural complications			
Animal bite	0 (0)	0 (0)	1 (1)
Arthropod bite	0 (0)	0 (0)	1 (1)
Arthropod sting	2 (2)	0 (0)	0 (0)
Asbestosis	1 (1)	0 (0)	0 (0)
Burns second degree	0 (0)	1 (1)	0 (0)
Chemical injury	0 (0)	0 (0)	1 (1)
Fall	10 (8)	17 (11)	12 (9)
Fibula fracture	1 (1)	0 (0)	0 (0)
Head injury	0 (0)	1 (1)	1 (1)
Heat exhaustion	0 (0)	0 (0)	1 (1)
Hypothermia	1 (1)	0 (0)	0 (0)
Injury	1 (1)	0 (0)	0 (0)
Joint injury	3 (3)	0 (0)	0 (0)
Laceration	1 (1)	1 (1)	4 (4)
Limb injury	1 (1)	1 (1)	2 (2)
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	0 (0)	1 (1)	2 (2)
Investigations			
Biopsy skin	0 (0)	0 (0)	1 (1)
Blood creatine increased	0 (0)	0 (0)	1 (1)
Blood creatinine abnormal	2 (2)	2 (2)	2 (2)
Blood glucose decreased	2 (2)	2 (2)	2 (2)
Blood glucose increased	2 (2)	1 (1)	0 (0)
Blood potassium decreased	1 (1)	1 (1)	0 (0)
Blood potassium increased	2 (2)	1 (1)	2 (2)
Blood testosterone decreased	1 (1)	0 (0)	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)
Hepatic enzyme increased	0 (0)	0 (0)	1 (1)
International normalised ratio increased	3 (2)	0 (0)	1 (1)
Laboratory test abnormal	1 (1)	2 (2)	2 (1)
Low density lipoprotein increased	1 (1)	0 (0)	0 (0)
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	2 (2)	1 (1)	1 (1)
Red blood cell count decreased	1 (1)	1 (1)	0 (0)
Weight decreased	1 (1)	0 (0)	1 (1)
Metabolism and nutrition disorders			
Abnormal weight gain	1 (1)	0 (0)	1 (1)
Acidosis	0 (0)	0 (0)	1 (1)
Decreased appetite	1 (1)	3 (3)	0 (0)
Dehydration	5 (4)	1 (1)	5 (5)
Fluid overload	0 (0)	0 (0)	1 (1)
Fluid retention	2 (2)	2 (2)	0 (0)
Haemochromatosis	0 (0)	0 (0)	1 (1)
Hypercholesterolaemia	9 (9)	5 (5)	6 (6)
Hyperkalaemia	2 (2)	2 (2)	2 (2)
Hyperlipidaemia	3 (3)	1 (1)	3 (2)
Hyperphosphataemia	1 (1)	1 (1)	0 (0)
Hypertriglyceridaemia	1 (1)	1 (1)	0 (0)
Hypocalcaemia	0 (0)	0 (0)	1 (1)
Hypokalaemia	3 (3)	1 (1)	0 (0)
Hypomagnesaemia	0 (0)	0 (0)	1 (1)
Hyponatraemia	1 (1)	0 (0)	0 (0)
Iron deficiency	1 (1)	1 (1)	2 (2)
Metabolic disorder	1 (1)	0 (0)	0 (0)
Obesity	1 (1)	0 (0)	1 (1)
Vitamin B12 deficiency	0 (0)	0 (0)	1 (1)
Vitamin D deficiency	2 (2)	0 (0)	6 (6)
Musculoskeletal and connective tissue disorders			
Ankle fracture	2 (2)	0 (0)	1 (1)
Arthralgia	7 (7)	6 (6)	8 (8)
Arthritis	0 (0)	1 (1)	2 (2)
Back pain	7 (7)	12 (11)	13 (11)
Bone pain	0 (0)	1 (1)	0 (0)
Bursitis	0 (0)	0 (0)	1 (1)
Coccydynia	0 (0)	1 (1)	0 (0)
Dupuytren's contracture	0 (0)	2 (1)	0 (0)
Exostosis	1 (1)	0 (0)	0 (0)
Facial bones fracture	0 (0)	0 (0)	1 (1)
Femur fracture	0 (0)	1 (1)	0 (0)
Fibromyalgia	0 (0)	0 (0)	2 (2)
Foot deformity	0 (0)	1 (1)	1 (1)
Foot fracture	4 (4)	4 (4)	0 (0)

Gout	1 (1)	1 (1)	1 (1)
Hand fracture	2 (2)	0 (0)	2 (1)
Hip fracture	0 (0)	0 (0)	1 (1)
Inclusion body myositis	1 (1)	0 (0)	0 (0)
Intervertebral disc protrusion	0 (0)	3 (2)	1 (1)
Ligament sprain	5 (4)	3 (2)	7 (6)
Lower limb fracture	0 (0)	1 (1)	0 (0)
Meniscus injury	0 (0)	1 (1)	1 (1)
Multiple fractures	3 (3)	1 (1)	3 (3)
Muscle spasms	2 (2)	4 (4)	0 (0)
Muscle strain	1 (1)	2 (2)	2 (2)
Muscular weakness	4 (4)	1 (1)	3 (3)
Musculoskeletal discomfort	1 (1)	2 (2)	0 (0)
Musculoskeletal pain	2 (2)	6 (6)	3 (3)
Myalgia	1 (1)	4 (3)	0 (0)
Neck pain	0 (0)	0 (0)	2 (2)
Neuropathic arthropathy	2 (1)	1 (1)	0 (0)
Osteoarthritis	2 (2)	3 (3)	5 (5)
Osteomyelitis	2 (2)	3 (3)	2 (2)
Pain in extremity	4 (4)	10 (8)	5 (5)
Pelvic fracture	1 (1)	0 (0)	0 (0)
Plantar fasciitis	2 (2)	0 (0)	0 (0)
Psoriatic arthropathy	0 (0)	0 (0)	1 (1)
Rheumatoid arthritis	1 (1)	3 (2)	0 (0)
Rib fracture	2 (2)	1 (1)	2 (2)
Rotator cuff syndrome	2 (2)	0 (0)	2 (2)
Tendon disorder	0 (0)	1 (1)	0 (0)
Tendonitis	2 (2)	0 (0)	1 (1)
Trigger finger	3 (3)	1 (1)	3 (3)
Upper limb fracture	2 (2)	1 (1)	1 (1)
Wrist fracture	2 (2)	2 (2)	0 (0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Neoplasm malignant	0 (0)	1 (1)	0 (0)
Polyp	0 (0)	2 (2)	2 (2)
Squamous cell carcinoma	2 (1)	1 (1)	0 (0)
Nervous system disorders			
Amnesia	0 (0)	2 (2)	0 (0)
Balance disorder	3 (2)	0 (0)	0 (0)
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)	0 (0)	7 (3)
Dementia Alzheimer's type	0 (0)	1 (1)	0 (0)
Diabetic neuropathy	2 (2)	8 (8)	5 (5)
Dizziness	9 (8)	7 (7)	9 (8)
Dysarthria	1 (1)	0 (0)	0 (0)
Encephalopathy	2 (2)	0 (0)	1 (1)
Epilepsy	0 (0)	0 (0)	1 (1)
Headache	18 (14)	18 (14)	13 (13)
Hemiparesis	1 (1)	0 (0)	0 (0)
Hypoaesthesia	1 (1)	1 (1)	1 (1)
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 injury	0 (0)	1 (1)	0 (0)
Neuropathy peripheral	2 (2)	3 (3)	6 (6)
Paraesthesia	0 (0)	1 (1)	0 (0)
Presyncope	1 (1)	4 (3)	1 (1)
Radiculitis brachial	0 (0)	0 (0)	1 (1)
Restless legs syndrome	1 (1)	0 (0)	1 (1)
Sciatica	1 (1)	1 (1)	1 (1)
Somnolence	1 (1)	0 (0)	0 (0)
Spinal column stenosis	1 (1)	0 (0)	1 (1)
Syncope	0 (0)	1 (1)	4 (4)
Tremor	0 (0)	0 (0)	1 (1)
VIIth nerve paralysis	4 (4)	0 (0)	1 (1)
Vertigo	5 (5)	4 (4)	1 (1)
Vestibular neuronitis	1 (1)	0 (0)	0 (0)
Psychiatric disorders			
Anxiety	5 (5)	6 (6)	4 (4)
Bipolar disorder	1 (1)	0 (0)	2 (2)
Dementia	0 (0)	0 (0)	2 (2)
Depression	5 (5)	4 (4)	4 (4)
Drug abuse	0 (0)	0 (0)	1 (1)
Insomnia	1 (1)	2 (2)	2 (2)
Mental disorder	1 (1)	1 (1)	0 (0)
Psychotic disorder	0 (0)	0 (0)	1 (1)
Schizoaffective disorder	0 (0)	0 (0)	1 (1)
Stress	0 (0)	1 (1)	0 (0)
Renal and urinary disorders			
Bladder cancer	0 (0)	1 (1)	0 (0)
Bladder prolapse	0 (0)	0 (0)	1 (1)
Bladder spasm	0 (0)	0 (0)	1 (1)

Cystitis	5 (4)	2 (2)	1 (1)
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)	3 (3)	0 (0)
Hydronephrosis	0 (0)	0 (0)	1 (1)
Hypertonic bladder	0 (0)	1 (1)	0 (0)
Kidney infection	1 (1)	1 (1)	2 (2)
Microalbuminuria	1 (1)	0 (0)	0 (0)
Micturition urgency	0 (0)	0 (0)	2 (2)
Nephrolithiasis	3 (3)	1 (1)	0 (0)
Nephropathy	1 (1)	3 (3)	2 (2)
Proteinuria	2 (2)	2 (2)	1 (1)
Renal failure	7 (7)	7 (6)	9 (8)
Renal failure acute	3 (3)	2 (2)	2 (2)
Renal failure chronic	7 (6)	2 (2)	9 (8)
Renal impairment	5 (5)	3 (3)	2 (2)
Urinary hesitation	0 (0)	1 (1)	0 (0)
Urinary incontinence	0 (0)	1 (1)	2 (2)
Urinary retention	0 (0)	0 (0)	1 (1)
Urinary tract infection	14 (13)	16 (13)	8 (7)
Reproductive system and breast disorders			
Benign prostatic hyperplasia	1 (1)	0 (0)	0 (0)
Breast cancer	0 (0)	1 (1)	0 (0)
Endometrial hyperplasia	0 (0)	1 (1)	0 (0)
Erectile dysfunction	0 (0)	0 (0)	2 (2)
Fibrocystic breast disease	0 (0)	0 (0)	1 (1)
Ovarian neoplasm	1 (1)	0 (0)	0 (0)
Prostatitis	0 (0)	0 (0)	1 (1)
Prostatomegaly	1 (1)	0 (0)	1 (1)
Uterine prolapse	0 (0)	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	3 (3)	1 (1)	3 (3)
Asthma	4 (4)	1 (1)	1 (1)
Bronchitis	9 (8)	14 (9)	8 (7)
Cardio-respiratory arrest	0 (0)	1 (1)	0 (0)
Chronic obstructive pulmonary disease	1 (1)	2 (2)	1 (1)
Chronic sinusitis	1 (1)	1 (1)	1 (1)
Cough	13 (13)	9 (7)	12 (9)
Dyspnoea	7 (7)	7 (5)	6 (4)
Epistaxis	4 (1)	1 (1)	1 (1)

Hypoxia	0 (0)	2 (2)	0 (0)
Nasal congestion	3 (3)	4 (4)	2 (2)
Nasal dryness	1 (1)	0 (0)	0 (0)
Nasopharyngitis	31 (27)	22 (20)	17 (16)
Oropharyngeal pain	1 (1)	5 (5)	2 (2)
Pharyngitis streptococcal	0 (0)	1 (1)	0 (0)
Pneumonia	7 (5)	6 (6)	10 (9)
Pulmonary embolism	0 (0)	0 (0)	1 (1)
Pulmonary fibrosis	1 (1)	0 (0)	0 (0)
Pulmonary hypertension	0 (0)	0 (0)	1 (1)
Pulmonary oedema	0 (0)	0 (0)	1 (1)
Respiratory distress	0 (0)	0 (0)	1 (1)
Respiratory tract congestion	0 (0)	1 (1)	1 (1)
Respiratory tract infection	3 (3)	2 (2)	2 (2)
Respiratory tract oedema	0 (0)	1 (1)	0 (0)
Rhinitis allergic	0 (0)	3 (3)	2 (2)
Sinusitis	13 (12)	8 (8)	20 (13)
Sleep apnoea syndrome	0 (0)	2 (2)	1 (1)
Sneezing	1 (1)	0 (0)	0 (0)
Upper respiratory tract infection	11 (10)	3 (3)	10 (10)
Wheezing	1 (1)	0 (0)	1 (1)
Skin and subcutaneous tissue disorders			
Actinic keratosis	0 (0)	0 (0)	2 (1)
Alopecia	1 (1)	1 (1)	2 (2)
Angioedema	0 (0)	0 (0)	1 (1)
Basal cell carcinoma	4 (4)	0 (0)	1 (1)
Blister	0 (0)	1 (1)	0 (0)
Cellulitis	9 (9)	11 (9)	4 (4)
Cellulitis gangrenous	0 (0)	1 (1)	0 (0)
Contusion	0 (0)	3 (3)	1 (1)
Dermal cyst	1 (1)	0 (0)	0 (0)
Dermatitis allergic	2 (2)	1 (1)	1 (1)
Dermatitis contact	1 (1)	1 (1)	0 (0)
Diabetic foot	1 (1)	4 (4)	7 (5)
Diabetic ulcer	0 (0)	0 (0)	1 (1)
Ecchymosis	1 (1)	0 (0)	0 (0)
Eczema	0 (0)	0 (0)	1 (1)
Excoriation	2 (2)	2 (2)	1 (1)
Furuncle	3 (2)	0 (0)	2 (2)
Herpes zoster	1 (1)	1 (1)	3 (3)
Hyperkeratosis	1 (1)	0 (0)	0 (0)
In-growing nail	0 (0)	1 (1)	0 (0)
Melanocytic naevus	0 (0)	0 (0)	1 (1)

Nail avulsion	0 (0)	0 (0)	1 (1)
Pruritus	2 (2)	2 (2)	0 (0)
Psoriasis	0 (0)	1 (1)	0 (0)
Rash	4 (4)	3 (3)	1 (1)
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	5 (5)	0 (0)	1 (1)
Skin lesion	1 (1)	0 (0)	3 (2)
Skin papilloma	1 (1)	0 (0)	2 (1)
Skin ulcer	4 (4)	2 (2)	0 (0)
Social circumstances			
Menopause	0 (0)	1 (1)	0 (0)
Surgical and medical procedures			
Cardiac pacemaker insertion	0 (0)	1 (1)	0 (0)
Cardiac pacemaker replacement	1 (1)	0 (0)	0 (0)
Foot amputation	0 (0)	1 (1)	0 (0)
Gastric bypass	1 (1)	0 (0)	0 (0)
Hip arthroplasty	0 (0)	0 (0)	1 (1)
Hyperbaric oxygen therapy	0 (0)	1 (1)	0 (0)
Inguinal hernia repair	1 (1)	0 (0)	0 (0)
Knee operation	0 (0)	0 (0)	1 (1)
Sinus operation	0 (0)	1 (1)	0 (0)
Skin lesion excision	1 (1)	0 (0)	0 (0)
Stent placement	0 (0)	2 (2)	0 (0)
Surgery	1 (1)	0 (0)	2 (2)
Toe amputation	0 (0)	1 (1)	1 (1)
Tooth extraction	5 (5)	3 (3)	3 (3)
Uterine dilation and curettage	1 (1)	0 (0)	0 (0)
Vascular disorders			
Aortic stenosis	1 (1)	0 (0)	0 (0)
Arteriovenous fistula	2 (1)	0 (0)	2 (2)
Basilar artery occlusion	0 (0)	0 (0)	1 (1)
Cerebrovascular accident	0 (0)	3 (3)	3 (2)
Deep vein thrombosis	0 (0)	1 (1)	0 (0)
Haematoma	2 (2)	1 (1)	0 (0)
Haemorrhagic stroke	0 (0)	0 (0)	1 (1)
Hypertension	28 (26)	18 (16)	27 (26)
Hypotension	2 (2)	0 (0)	2 (2)
Ischaemic stroke	0 (0)	1 (1)	3 (3)
Orthostatic hypotension	1 (1)	1 (1)	0 (0)
Peripheral vascular disorder	2 (1)	2 (2)	1 (1)
Poor peripheral circulation	0 (0)	0 (0)	1 (1)

Raynaud's phenomenon	1 (1)	0 (0)	0 (0)
Transient ischaemic attack	0 (0)	1 (1)	4 (4)
Venous insufficiency	0 (0)	1 (1)	2 (1)
Venous stenosis	1 (1)	0 (0)	1 (1)

*One year visit (If the 1 year visit was not completed or if it was completed prior to 365 days, then 365 days was used).

†Based on medical monitor using Medical Dictionary for Regulatory Activities coding.

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