Supplemental Online Content

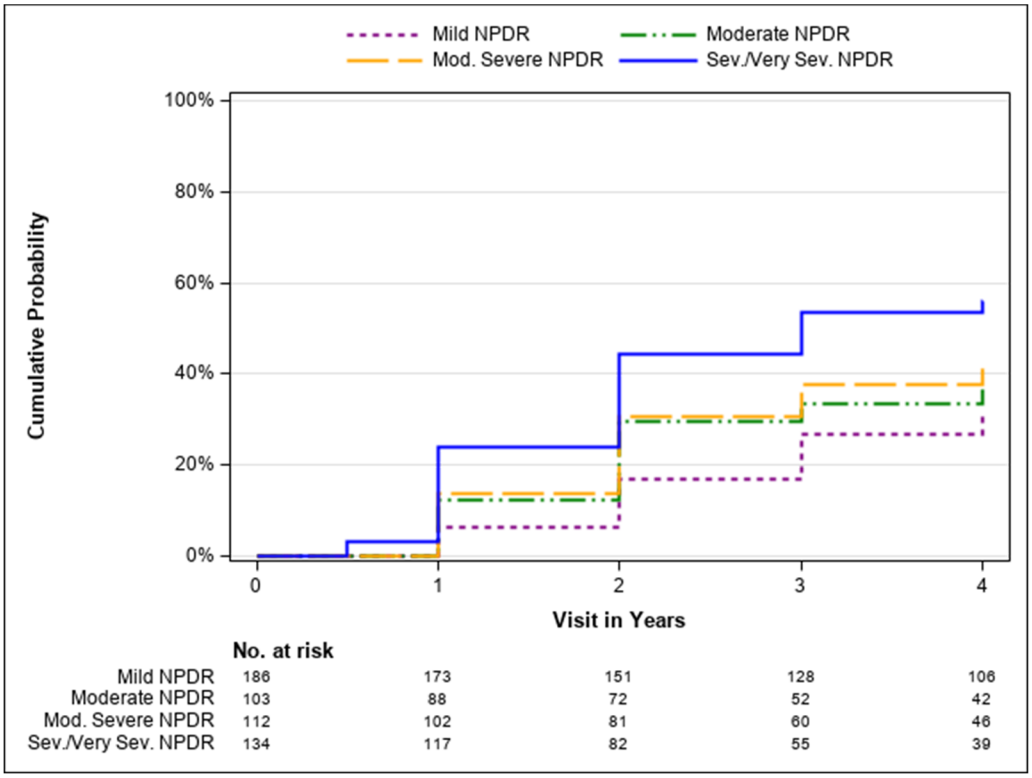
Marcus DM, Silva PS, Liu D, et al; DRCR Retina Network. Association of predominantly peripheral lesions on ultra-widefield imaging and the risk of diabetic retinopathy worsening over time. *JAMA Ophthalmol*. Published online August 18, 2022. doi:10.1001/jamaophthalmol.2022.3131

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

Abbreviations

Abbreviation	Definition
ACR	Albumin creatinine ratio
CI	Confidence interval
CME	Cystoid macular edema
CST	Central subfield thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
EGFR	Estimated glomerular filtration rate
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
H/MA	Hemorrhages and/or microaneurysms
HbA1c	Hemoglobin A1c
IPW	Inverse probability weighted
IRMA	Intraretinal microvascular anomalies
NPDR	Non-proliferative diabetic retinopathy
NVE	New vessels/neovascularization elsewhere
OCT	Optical coherence tomography
PC IOL	Posterior chamber intraocular lenses
PDR	Proliferative diabetic retinopathy
PPL	Predominantly peripheral lesions
PRP	Panretinal photocoagulation
UWF	Ultrawide field
VB	Venous beading
VEGF	Vascular endothelial growth factor

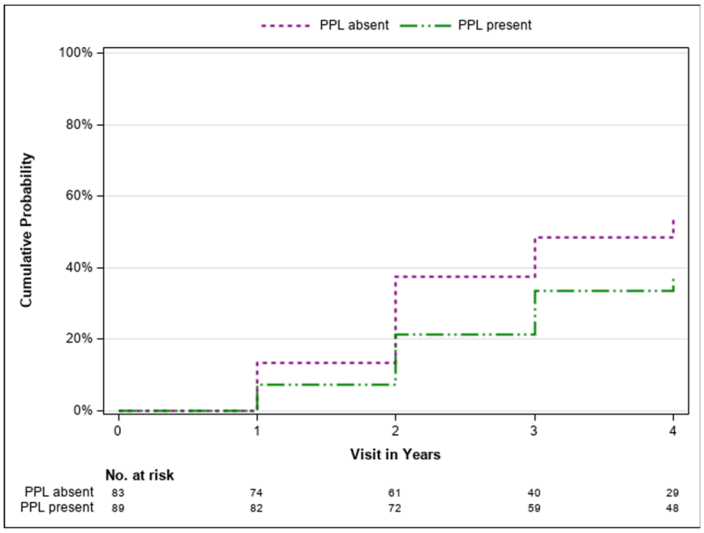
eFigure 1. Cumulative proportion of disease worsening (DRSS worsening by 2 or more steps within the ETDRS fields on masked UWF-color images or receipt of DR treatment) through 4 years by baseline DRSS level on standard ETDRS fundus photographs



Stratified by the baseline DRSS level from the standard ETDRS fundus photographs. Two or more step DRSS worsening was determined within the ETDRS fields on the UWF-color images. Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR were censored after treatment initiation. Eyes not meeting the primary outcome or receiving non-DR treatment were censored at the last visit. The cumulative proportion (95% confidence interval) of primary outcome was 31% (24%, 39%) in eyes with baseline mild NPDR, 37% (27%, 48%) with moderate NPDR, 43% (34%, 54%) with moderately severe NPDR, and 56% (47%, 65%) with severe or very severe NPDR.

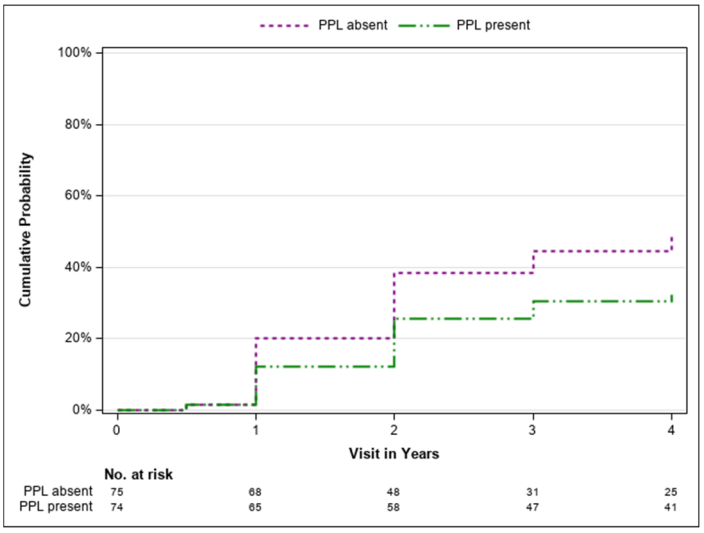
eFigure 2. Stratified Analyses of Primary Outcome: DRSS worsening by 2 or more steps within the ETDRS fields on masked UWF-color images or receipt of DR treatment through 4 years by baseline DRSS level on UWF-color and color-PPL

A) Mild NPDR (Level 35)



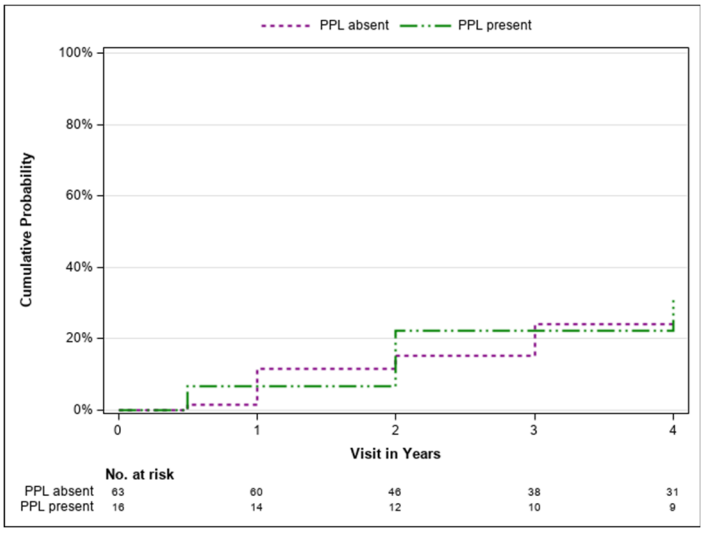
	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI*)
Color-PPL Absent	83	54% (42%, 66%)	0.61 (0.39, 0.94)
Color-PPL Present	89	38% (28%, 49%)	

B) Moderate NPDR (Level 43)



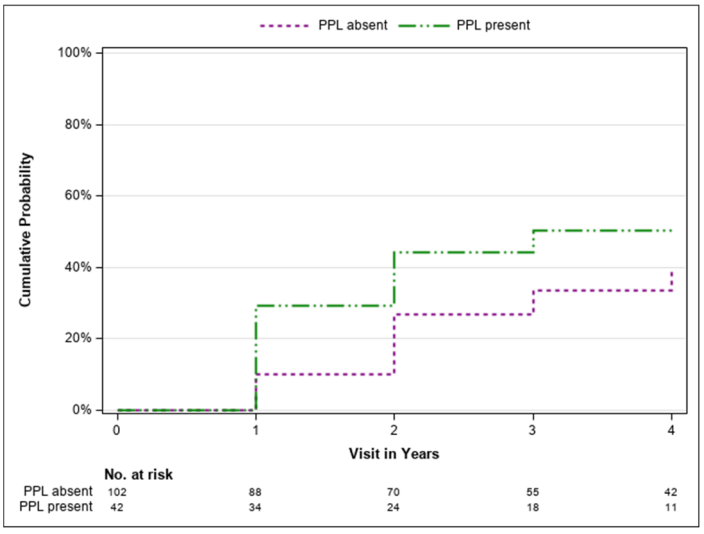
	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI*)
Color-PPL Absent	75	49% (37%, 63%)	0.57 (0.34, 0.69)
Color-PPL Present	74	32% (22%, 45%)	

C) Moderately Severe NPDR (Level 47)



	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI*)
Color-PPL Absent	63	24% (15%, 38%)	1.21 (0.40, 3.66)
Color-PPL Present	16	31% (13%, 63%)	

D) Severe or Very Severe NPDR (Level 53)

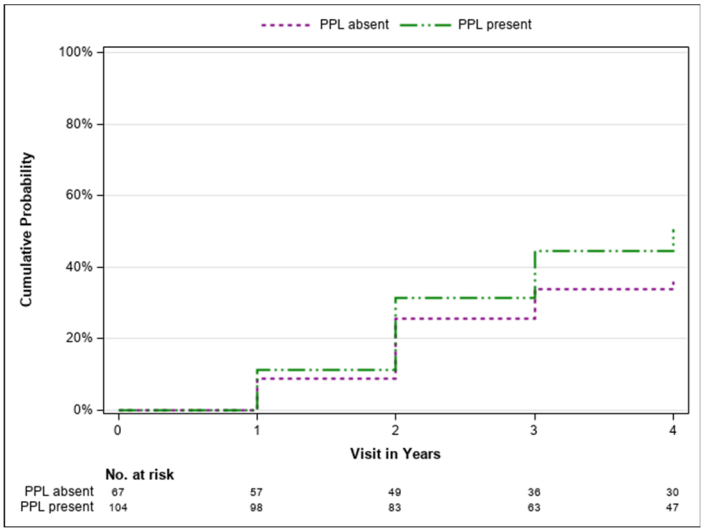


	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI*)
Color-PPL Absent	102	40% (30%, 52%)	1.64 (0.93, 2.90)
Color-PPL Present	42	50% (35%, 68%)	

* *P* = .02 for interaction between DRSS level and color-PPL in the overall cohort.

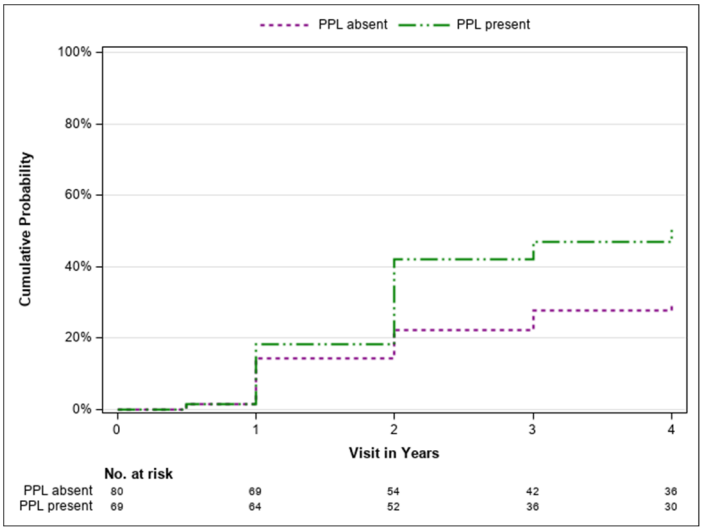
eFigure 3. Stratified Analyses of Primary Outcome: DRSS worsening by 2 or more steps within the ETDRS fields on masked UWF-color images or receipt of DR treatment through 4 years by baseline DRSS level on UWF-color and FA-PPL

A) Mild NPDR (Level 35)



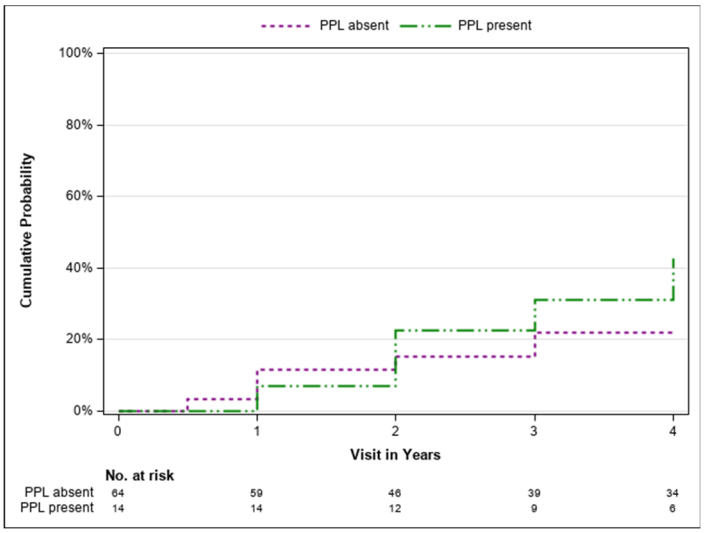
	No. of Eyes	Kaplan-Meier Estimates (95% CI)
FA-PPL Absent	67	36% (25%, 51%)
FA-PPL Present	104	50% (41%, 61%)

B) Moderate NPDR (Level 43)



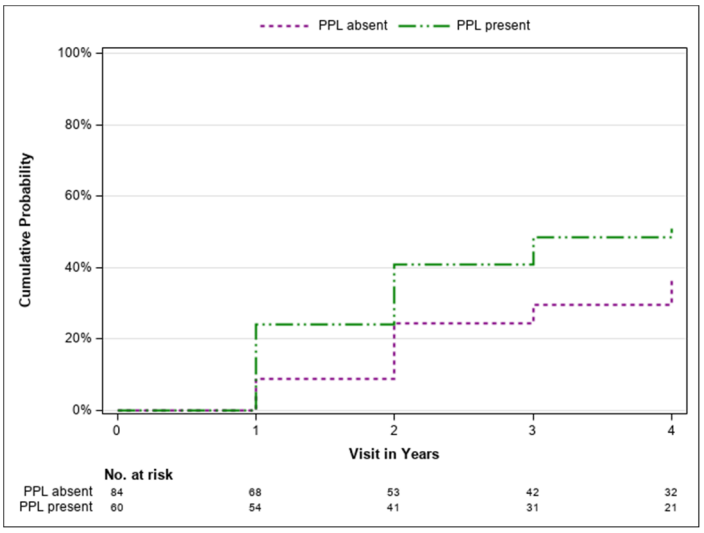
	No. of Eyes	Kaplan-Meier Estimates (95% CI)
FA-PPL Absent	80	30% (20%, 43%)
FA-PPL Present	69	50% (39%, 63%)

C) Moderately Severe NPDR (Level 47)



	No. of Eyes	Kaplan-Meier Estimates (95% CI)
FA-PPL Absent	64	22% (13%, 35%)
FA-PPL Present	14	43% (20%, 76%)

D) Severe or Very Severe NPDR (Level 53)



	No. of Eyes	Kaplan-Meier Estimates (95% CI)
FA-PPL Absent	84	36% (25%, 50%)
FA-PPL Present	60	51% (38%, 65%)

P = .92 for interaction between DRSS level and FA-PPL in the overall cohort

eTable 1. Visit Completion Over 4 Years

	All Eyes		By Color-PPL [a]				By FA-PPL [b]			
			Color-PPL Absent		Color-PPL Present		FA-PPL Absent		FA-PPL Present	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
All Study Eyes	**544**	**(100%)**	**323**	**(100%)**	**221**	**(100%)**	**295**	**(100%)**	**247**	**(100%)**
Year 1										
Completed [c]	**481**	**(88%)**	**289**	**(89%)**	**192**	**(87%)**	**255**	**(86%)**	**224**	**(91%)**
Died	9	(2%)	5	(2%)	4	(2%)	4	(1%)	5	(2%)
Lost to follow up or withdrew	36	(7%)	21	(7%)	15	(7%)	28	(9%)	8	(3%)
Missed [d]	18	(3%)	8	(2%)	10	(5%)	8	(3%)	10	(4%)
Year 2										
Completed [c]	**456**	**(84%)**	**270**	**(84%)**	**186**	**(84%)**	**235**	**(80%)**	**219**	**(89%)**
Died	15	(3%)	11	(3%)	4	(2%)	10	(3%)	5	(2%)
Lost to follow up or withdrew	59	(11%)	36	(11%)	23	(10%)	44	(15%)	15	(6%)
Missed [d]	14	(3%)	6	(2%)	8	(4%)	6	(2%)	8	(3%)
Year 3										
Completed [c]	**426**	**(78%)**	**242**	**(75%)**	**184**	**(83%)**	**216**	**(73%)**	**210**	**(85%)**
Died	23	(4%)	17	(5%)	6	(3%)	13	(4%)	10	(4%)
Lost to follow up or withdrew	78	(14%)	49	(15%)	29	(13%)	56	(19%)	20	(8%)
Missed [d]	17	(3%)	15	(5%)	2	(<1%)	10	(3%)	7	(3%)
Year 4										
Completed [c]	**389**	**(72%)**	**223**	**(69%)**	**166**	**(75%)**	**205**	**(69%)**	**184**	**(74%)**
Died	38	(7%)	26	(8%)	12	(5%)	14	(5%)	24	(10%)
Lost to follow up or withdrew	112	(21%)	71	(22%)	41	(19%)	75	(25%)	35	(14%)
Missed [e]	5	(<1%)	3	(<1%)	2	(<1%)	1	(<1%)	4	(2%)

[a] Includes study eyes with gradable baseline color-PPL status and baseline DRSS level 35-53.

[b] Includes study eyes with gradable baseline FA-PPL status and baseline DRSS level 35-53 (i.e., 2 eyes excluded due to ungradable FA-PPL).

[c] Counts all participants who completed the visit within the following windows (±0.5 years from the target): 183-547 days for 1-year visit, 548-912 days for 2-year visit, 913-1277 days for 3-year visit, and 1278-1642 days for 4-year visit. Numbers died and lost to follow up or withdrawn are cumulative.

[d] Includes participants who completed the visit outside of the analysis window or completed a phone-call visit after missing the annual visit.

[e] Eyes completing the visit outside the window were considered having missed the visit.

eTable 2. Baseline Characteristics by Baseline PPL Status

	By Baseline Color- PPL				By Baseline FA-PPL			
All Study Eyes	**Color-PPL Absent**		**Color-PPL Present**		**FA-PPL Absent**		**FA-PPL Present**	
No. of Eyes	323		221		295		247	
Participant Characteristics								
Females, N (%)	149	(46%)	115	(52%)	125	(42%)	137	(55%)
Age (years), Median (IQR)	61	(52, 69)	62	(53, 68)	60	(51, 68)	63	(54, 70)
Race/Ethnicity, N (%)								
White	211	(65%)	162	(73%)	194	(66%)	178	(72%)
Black/African American	58	(18%)	36	(16%)	52	(18%)	42	(17%)
Hispanic or Latino	37	(11%)	13	(6%)	36	(12%)	13	(5%)
Asian	9	(3%)	5	(2%)	7	(2%)	7	(3%)
More than one race	4	(1%)	2	(<1%)	2	(<1%)	4	(2%)
Native Hawaiian/Other Pacific Islander	0	(0%)	1	(<1%)	1	(<1%)	0	(0%)
Unknown/not reported	4	(1%)	2	(<1%)	3	(1%)	3	(1%)
Diabetes Type, N (%)								
Type 1	26	(8%)	56	(25%)	29	(10%)	53	(21%)
Type 2	292	(90%)	164	(74%)	261	(88%)	193	(78%)
Uncertain	5	(2%)	1	(<1%)	5	(2%)	1	(<1%)
Duration of Diabetes (years), Median (IQR)	17	(12, 25)	24	(16, 31)	17	(12, 25)	23	(16, 30)
Hemoglobin A_{1c} (%), Median (IQR) [a]	8.1	(7.0, 9.5)	7.8	(7.1, 8.7)	8.0	(7.1, 9.3)	7.9	(7.0, 8.9)
Insulin Used, N (%)	233	(72%)	169	(76%)	210	(71%)	190	(77%)
Mean Arterial Pressure (mmHg), Median (IQR)	97	(91, 108)	96	(88, 103)	99	(92, 108)	94	(89, 102)
History of Hypertension, N (%)	244	(76%)	175	(79%)	223	(76%)	194	(79%)
History of High Cholesterol/Dyslipidemia, N (%)	220	(68%)	152	(69%)	201	(68%)	169	(68%)
Taking Fenofibrate at Baseline, N (%)	13	(4%)	9	(4%)	12	(4%)	10	(4%)
Taking Metformin at Baseline, N (%) [b]	155	(50%)	91	(42%)	137	(49%)	108	(45%)
EGFR (mL/min/1.73 m^2) [c]								
Median (IQR)	87	(61, 90)	90	(64, 90)	89	(63, 90)	86	(63, 90)
< 60, N (%)	42	(13%)	24	(11%)	36	(12%)	30	(12%)
≥ 60, N (%)	149	(46%)	100	(45%)	140	47%)	108	(44%)
Unknown, N (%)	132	(41%)	97	(44%)	119	40%)	109	(44%)
Albumin Creatinine Ratio [c]								
Median (IQR)	29	(11, 155)	12	(4, 69)	27	(7, 112)	19	(7, 63)
No albuminuria (<30), N (%)	99	(31%)	80	(36%)	97	(33%)	82	(33%)
Microalbuminuria (30-300), N (%)	59	(18%)	33	(15%)	50	(17%)	41	(17%)
Macroalbuminuria (>300), N (%)	32	(10%)	9	(4%)	27	(9%)	14	(6%)
Unknown, N (%)	133	(41%)	99	(45%)	121	(41%)	110	(45%)
Participants with Two Study Eyes, N (%)	212	(66%)	142	(64%)	197	(67%)	157	(64%)
Study Eye Ocular Characteristics								
Visual Acuity Letter Score, Median (IQR)	86	(89, 81)	86	(90, 82)	85	(89, 82)	87	(90, 81)
Snellen equivalent, Median (IQR)	20/20	(20/16, 20/25)	20/20	(20/16, 20/25)	20/20	(20/16, 20/25)	20/20	(20/16, 20/25)
DRSS Level by Reading Center Assessment (UWF Masked), N (%)								
Mild NPDR (Level 35)	83	(26%)	89	(40%)	67	(23%)	104	(42%)
Moderate NPDR (Level 43)	75	(23%)	74	(33%)	80	(27%)	69	(28%)
Moderately Severe NPDR (Level 47)	63	(20%)	16	(7%)	64	(22%)	14	(6%)
Severe and Very Severe NPDR (Level 53)	102	(32%)	42	(19%)	84	(28%)	60	(24%)

All Study Eyes	By Baseline Color- PPL				By Baseline FA-PPL			
	Color-PPL Absent		Color-PPL Present		FA-PPL Absent		FA-PPL Present	
No. of Eyes	323		221		295		247	
DRSS Level by Reading Center Assessment (UWF Unmasked), N (%)								
Mild NPDR (Level 35)	79	(24%)	59	(27%)	60	(20%)	77	(31%)
Moderate NPDR (Level 43)	76	(24%)	57	(26%)	74	(25%)	59	(24%)
Moderately Severe NPDR (Level 47)	66	(20%)	37	(17%)	64	(22%)	38	(15%)
Severe and Very Severe NPDR (Level 53)	99	(31%)	59	(27%)	93	(32%)	65	(26%
Inactive PDR (Level 60) or Mild PDR (Level 61)	2	(<1%)	4	(2%)	3	(1%)	3	(1%)
Moderate PDR (Level 65)	0	(0%)	5	(2%)	0	(0%)	5	(2%)
Ungradable	1	(<1%)	0	(0%)	1	(<1%)	0	(0%)
Difference in DRSS Level by Reading Center Assessment (UWF Unmasked vs. Masked), N (%) [d]								
UWF unmasked worse	12	(4%)	74	(33%)	28	(10%)	58	(23%)
Same grading	306	(95%)	144	(65%)	262	(89%)	186	(75%)
UWF masked worse	4	(1%)	3	(1%)	4	(1%)	3	(1%)
Lens Status, N (%)								
Aphakic	1	(<1%)	0	(0%)	1	(<1%)	0	(0%)
PC IOL	76	(24%)	58	(26%)	54	(18%)	79	(32%)
Phakic	246	(76%)	163	(74%)	240	(81%)	168	(68%)
OCT CST Spectralis Equivalent (µm), Median (IQR) [e]	278	(259, 295)	276	(262, 295)	279	(263, 297)	275	(255, 294)
OCT Volume (mm^2), Median (IQR) [f]	7.0	(6.6, 7.3)	6.9	(6.6, 7.3)	7.1	(6.7, 7.4)	6.8	(6.5, 7.2)
History of DME Treatment, N (%)	58	(18%)	61	(28%)	55	(19%)	64	(26%)
Focal laser	54	(17%)	60	(27%)	54	(18%)	60	(24%)
Anti-VEGF	22	(7%)	9	(4%)	14	(5%)	17	(7%)
Corticosteroids (including implants)	5	(2%)	0	(0%)	4	(1%)	1	(<1%)
Predominantly Peripheral Lesions on UWF-Color, N (%)	--	--	--	--	85	(29%)	136	(55%)
Predominantly Peripheral Lesions on UWF-FA, N (%) [g]	111	(35%)	136	(62%)	--	--	--	--

[a] Unavailable for 4 eyes without color-PPL and 3 with color-PPL; 2 eyes without FA-PPL and 5 with FA-PPL.

[b] Unavailable for 16 eyes without color-PPL and 2 with color-PPL;13 eyes without FA-PPL, and 5 with FA-PPL. Percentage is based on eyes with available information.

[c] Blood and urine samples were implemented approximately five months after study recruitment began.

[d] Excluding one eye (without color-PPL and FA-PPL) with ungradable unmasked grade. Percentage is based on eyes with available information.

[e] Cirrus measurements were converted to Spectralis equivalents using the following formula: Spectralis = 40.78 + 0.95 × Cirrus.

[f] Retinal volume measurements were converted to Stratus equivalents using the following formulae: Stratus = -1.21 + 1.02 × Cirrus; Stratus = -2.05 + 1.06 × Spectralis.

[g] FA-PPL were ungradable for 2 eyes. Percentage is based on eyes with available information.

eTable 3. Baseline Characteristics by 4-Year Visit Completion

	By 4-Year Visit Completion			
	Non-Completers		**Completers**	
No. of Participants	106		261	
Participant Characteristics				
Females, N (%)	56	(53%)	126	(48%)
Age (years), Median (IQR)	62	(51, 69)	62	(54, 69)
Race/Ethnicity, N (%)				
White	70	(66%)	179	(69%)
Black/African American	21	(20%)	47	(18%)
Hispanic or Latino	12	(11%)	20	(8%)
Asian	1	(<1%)	9	(3%)
More than one race	1	(<1%)	2	(<1%)
Native Hawaiian/Other Pacific Islander	0	(0%)	1	(<1%)
Unknown/not reported	1	(<1%)	3	(1%)
Diabetes Type, N (%)				
Type 1	10	(9%)	40	(15%)
Type 2	95	(90%)	218	(84%)
Uncertain	1	(<1%)	3	(1%)
Duration of Diabetes (years), Median (IQR)	17	(12, 26)	21	(14, 28)
Hemoglobin A_{1c} (%), Median (IQR) [a]	8.1	(7.2, 9.2)	7.8	(7.0, 9.0)
Insulin Used, N (%)	73	(69%)	192	(74%)
Mean Arterial Pressure (mmHg), Median (IQR)	97	(90, 107)	97	(91, 105)
History of Hypertension, N (%)	79	(75%)	208	(80%)
History of High Cholesterol/Dyslipidemia, N (%)	73	(69%)	184	(70%)
Taking Fenofibrate at Baseline, N (%)	9	(8%)	6	(2%)
Taking Metformin at Baseline, N (%) [b]	40	(40%)	130	(51%)
Estimated Glomerular Filtration Rate (mL/min/1.73 m^2) [c]				
Median (IQR)	81	(48, 90)	88	(63, 90)
< 60, N (%)	17	(16%)	32	(12%)
≥ 60, N (%)	39	(37%)	124	(48%)
Unknown, N (%)	50	(47%)	105	(40%)
Albumin Creatinine Ratio [c]				
Median (IQR)	46	(12, 148)	20	(7, 77)
No albuminuria (<30), N (%)	25	(24%)	92	(35%)
Microalbuminuria (30-300), N (%)	21	(20%)	42	(16%)
Macroalbuminuria (>300), N (%)	10	(9%)	19	(7%)
Unknown, N (%)	50	(47%)	108	(41%)
Participants with two study eyes, N (%)	49	(46%)	128	(49%)
Study Eye Ocular Characteristics				
No. of Study Eyes	155		389	
Visual Acuity Letter Score, Median (IQR)	84	(88, 79)	86	(90, 82)
Snellen equivalent, Median (IQR)	20/20	(20/20, 20/25)	20/20	(20/16, 20/25)
DRSS Level by Reading Center Assessment (UWF Masked), N (%)				
Mild NPDR (Level 35)	46	(30%)	126	(32%)
Moderate NPDR (Level 43)	39	(25%)	110	(28%)
Moderately Severe NPDR (Level 47)	19	(12%)	60	(15%)
Severe and Very Severe NPDR (Level 53)	51	(33%)	93	(24%)
DRSS Level by Reading Center Assessment (UWF Unmasked), N (%)				
Mild NPDR (Level 35)	40	(26%)	98	(25%)
Moderate NPDR (Level 43)	32	(21%)	101	(26%)

	By 4-Year Visit Completion			
	Non-Completers		Completers	
Moderately Severe NPDR (Level 47)	28	(18%)	75	(19%)
Severe and Very Severe NPDR (Level 53)	52	(34%)	106	(27%)
Inactive PDR (Level 60) or Mild PDR (Level 61)	3	(2%)	3	(<1%)
Moderate PDR (Level 65)	0	(0%)	5	(1%)
Ungradable	0	(0%)	1	(<1%)
Difference in DRSS Level by Reading Center Assessment (UWF Unmasked vs. Masked), N (%)				
UWF unmasked worse	21	(14%)	65	(17%)
Same grading	130	(84%)	320	(82%)
UWF masked worse	4	(3%)	3	(<1%)
Lens Status, N (%)				
Aphakic	0	(0%)	1	(<1%)
PC IOL	39	(25%)	95	(24%)
Phakic	116	(75%)	293	(75%)
OCT CST Spectralis Equivalent (µm), Median (IQR) [f]	274	(255, 293)	279	(263, 296)
OCT Volume (mm^2), Median (IQR) [f]	7.0	(6.6, 7.3)	6.9	(6.6, 7.3)
History of DME Treatment, N (%)	20	(13%)	99	(25%)
Focal laser	20	(13%)	94	(24%)
Anti-VEGF	7	(5%)	24	(6%)
Corticosteroids (including implants)	1	(<1%)	4	(1%)
Predominantly Peripheral Lesions on UWF-Color, N (%)	55	(35%)	166	(43%)
Predominantly Peripheral Lesions on UWF-FA, N (%) [g]	63	(41%)	184	(47%)

[a] Unavailable for 6 participants (2 non-completers and 4 completers)

[b] Unavailable for 6 non-completers and 5 completers. Percentage is based on participants with available information

[c] Blood and urine samples were implemented approximately five months after study recruitment began.

[d] Excluding one eye with ungradable unmasked grade. % Percentage based on eyes with available information.

[e] Cirrus measurements were converted to Spectralis equivalents using the following formula: Spectralis = 40.78 + 0.95 × Cirrus.

[f] Retinal volume measurements were converted to Stratus equivalents using the following formulae: Stratus = -1.21 + 1.02 × Cirrus; Stratus = -2.05 + 1.06 × Spectralis.

[g] FA-PPL were ungradable for 2 eyes. Percentage is based on eyes with available information.

eTable 4. Comparison of Baseline PPL on UWF-Color and UWF-FA Images

	PPL Characteristics on UWF-FA [a]		
PPL Characteristics on UWF-color image [a]			
PPL Status, N (%)	**Absent**	**Present**	**Total**
Absent	210 (39%)	111 (20%)	321 (59%)
Present	85 (16%)	136 (25%)	221 (41%)
Total	295 (54%)	247 (46%)	542 (100%)
PPL Status for H/Ma, N (%)	**Absent**	**Present**	**Total**
Absent	248 (46%)	111 (21%)	359 (67%)
Present	66 (12%)	114 (21%)	180 (33%)
Total	314 (58%)	225 (42%)	539 (100%)
PPL Status for IRMA, N (%)	**Absent**	**Present**	**Total**
Absent	367 (69%)	79 (15%)	446 (84%)
Present	53 (10%)	31 (6%)	84 (16%)
Total	420 (79%)	110 (21%)	530 (100%)
PPL Status for VB, N (%)	**Absent**	**Present**	**Total**
Absent	528 (99%)	3 (<1%)	531 (>99%)
Present	4 (<1%)	1 (<1%)	5 (<1%)
Total	532 (>99%)	4 (<1%)	536 (100%)
PPL Status for NVE, N (%)	**Absent**	**Present**	**Total**
Absent	510 (94%)	24 (4%)	534 (99%)
Present	2 (<1%)	6 (1%)	8 (1%)
Total	512 (94%)	30 (6%)	542 (100%)
PPL Status in Field 3, N (%)	**Absent**	**Present**	**Total**
Absent	365 (68%)	81 (15%)	446 (83%)
Present	35 (7%)	54 (10%)	89 (17%)
Total	400 (75%)	135 (25%)	535 (100%)
PPL Status in Field 4, N (%)	**Absent**	**Present**	**Total**
Absent	350 (66%)	90 (17%)	440 (83%)
Present	30 (6%)	63 (12%)	93 (17%)
Total	380 (71%)	153 (29%)	533 (100%)
PPL Status in Field 5, N (%)	**Absent**	**Present**	**Total**
Absent	382 (73%)	69 (13%)	451 (86%)
Present	38 (7%)	36 (7%)	74 (14%)
Total	420 (80%)	105 (20%)	525 (100%)
PPL Status in Field 6, N (%)	**Absent**	**Present**	**Total**
Absent	330 (62%)	118 (22%)	448 (84%)
Present	42 (8%)	43 (8%)	85 (16%)
Total	372 (70%)	161 (30%)	533 (100%)
PPL Status in Field 7, N (%)	**Absent**	**Present**	**Total**
Absent	352 (71%)	86 (17%)	438 (88%)
Present	44 (9%)	14 (3%)	58 (12%)
Total	396 (80%)	100 (20%)	496 (100%)

	PPL Characteristics on UWF-FA [a]			
PPL Characteristics on UWF-color image [a]				
Number of peripheral fields with PPL, N (%)	**No FA-PPL**	**FA-PPL in 1 Field**	**FA-PPL in ≥2 Fields**	**Total**
No PPL	210 (39%)	50 (9%)	61 (11%)	321 (59%)
PPL in 1 Field	60 (11%)	19 (4%)	39 (7%)	118 (22%)
PPL in ≥2 Fields	25 (5%)	6 (1%)	72 (13%)	103 (19%)
Total	295 (54%)	75 (14%)	172 (32%)	542 (100%)

[a] Limited to eyes with gradable color-PPL and FA-PPL in each region.

eTable 5. Treatment Initiation During Follow-up by Baseline DRSS Level

Treatment During Follow-up	By Baseline Color-PPL				By Baseline FA-PPL			
	Color-PPL Absent		Color-PPL Present		FA-PPL Absent		FA-PPL Present	
Overall								
No. of Eyes	**323**		**221**		**295**		**247**	
Received Treatment for DR or DME, N (%)	**72**	**(22%)**	**26**	**(12%)**	**62**	**(21%)**	**35**	**(14%)**
Received Treatment for DR, N (%)	**37**	**(11%)**	**21**	**(10%)**	**31**	**(11%)**	**26**	**(11%)**
PRP	19	(6%)	17	(8%)	19	(6%)	17	(7%)
Anti-VEGF	23	(7%)	12	(5%)	19	(6%)	15	(6%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	3	(1%)	1	(0%)	2	(1%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Received Treatment for DME, N (%)	**58**	**(18%)**	**16**	**(7%)**	**51**	**(17%)**	**22**	**(9%)**
Focal Laser	20	(6%)	7	(3%)	17	(6%)	10	(4%)
Anti-VEGF	47	(15%)	10	(5%)	42	(14%)	14	(6%)
Steroid	0	(0%)	1	(0%)	1	(0%)	0	(0%)
Vitrectomy	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Other [a]	1	(0%)	1	(0%)	1	(0%)	1	(0%)
Received Anti-VEGF, Steroid, or Vitrectomy for Conditions Other Than DR or DME, N (%) [b]	**6**	**(2%)**	**2**	**(1%)**	**5**	**(2%)**	**3**	**(1%)**
Mild NPDR (Level 35)								
No. of Eyes	**83**		**89**		**67**		**104**	
Received Treatment for DR or DME, N (%)	**9**	**(11%)**	**5**	**(6%)**	**8**	**(12%)**	**6**	**(6%)**
Received Treatment for DR, N (%)	**3**	**(4%)**	**2**	**(2%)**	**3**	**(4%)**	**2**	**(2%)**
PRP	3	(4%)	2	(2%)	3	(4%)	2	(2%)
Anti-VEGF	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Received Treatment for DME, N (%)	**7**	**(8%)**	**3**	**(3%)**	**5**	**(7%)**	**5**	**(5%)**
Focal Laser	4	(5%)	3	(3%)	4	(6%)	3	(3%)
Anti-VEGF	4	(5%)	1	(1%)	3	(4%)	2	(2%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Received Anti-VEGF, Steroid, or Vitrectomy for Conditions Other Than DR or DME, N (%)	**0**	**(0%)**	**0**	**(0%)**	**0**	**(0%)**	**0**	**(0%)**
Moderate NPDR (Level 43)								
No. of Eyes	**75**		**74**		**80**		**69**	
Received Treatment for DR or DME, N (%)	**19**	**(25%)**	**4**	**(5%)**	**14**	**(18%)**	**9**	**(13%)**
Received Treatment for DR, N (%)	**7**	**(9%)**	**4**	**(5%)**	**5**	**(6%)**	**6**	**(9%)**
PRP	4	(5%)	3	(4%)	2	(3%)	5	(7%)
Anti-VEGF	3	(4%)	3	(4%)	3	(4%)	3	(4%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)

Treatment During Follow-up	By Baseline Color-PPL				By Baseline FA-PPL			
	Color-PPL Absent		Color-PPL Present		FA-PPL Absent		FA-PPL Present	
Received Treatment for DME, N (%)	**16**	**(21%)**	**2**	**(3%)**	**13**	**(16%)**	**5**	**(7%)**
Focal Laser	7	(9%)	0	(0%)	4	(5%)	3	(4%)
Anti-VEGF	13	(17%)	1	(1%)	11	(14%)	3	(4%)
Steroid	0	(0%)	1	(1%)	1	(1%)	0	(0%)
Vitrectomy	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Other [a]	1	(1%)	1	(1%)	1	(1%)	1	(1%)
Received Anti-VEGF, Steroid, or Vitrectomy for Conditions Other Than DR or DME, N (%)	**2**	**(3%)**	**1**	**(1%)**	**3**	**(4%)**	**0**	**(0%)**
Moderately Severe NPDR (Level 47)								
No. of Eyes	**63**		**16**		**64**		**14**	
Received Treatment for DR or DME, N (%)	**15**	**(24%)**	**4**	**(25%)**	**14**	**(22%)**	**4**	**(29%)**
Received Treatment for DR, N (%)	**10**	**(16%)**	**4**	**(25%)**	**9**	**(14%)**	**4**	**(29%)**
PRP	7	(11%)	3	(19%)	7	(11%)	3	(21%)
Anti-VEGF	6	(10%)	3	(19%)	6	(9%)	2	(14%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	1	(6%)	1	(2%)	0	(0%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Received Treatment for DME, N (%)	**12**	**(19%)**	**3**	**(19%**	**12**	**(19%)**	**2**	**(14%)**
Focal Laser	2	(3%)	0	(0%)	1	(2%)	1	(7%)
Anti-VEGF	11	(17%)	3	(19%)	11	(17%)	2	(14%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Received Anti-VEGF, Steroid, or Vitrectomy for Conditions Other Than DR or DME, N (%)	**1**	**(2%)**	**0**	**(0%)**	**0**	**(0%)**	**1**	**(7%)**
Severe and Very Severe NPDR (Level 53)								
No. of Eyes	**102**		**42**		**84**		**60**	
Received Treatment for DR or DME, N (%)	**29**	**(28%)**	**13**	**(31%)**	**26**	**(31%)**	**16**	**(27%)**
Received Treatment for DR, N (%)	**17**	**(17%)**	**11**	**(26%)**	**14**	**(17%)**	**14**	**(23%)**
PRP	5	(5%)	9	(21%)	7	(8%)	7	(12%)
Anti-VEGF	14	(14%)	5	(12%)	10	(12%)	9	(15%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	1	(2%)	0	(0%)	1	(2%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Received Treatment for DME, N (%)	**23**	**(23%)**	**8**	**(19%)**	**21**	**(25%)**	**10**	**(17%)**
Focal Laser	7	(7%)	4	(10%)	8	(10%)	3	(5%)
Anti-VEGF	19	(19%)	5	(12%)	17	(20%)	7	(12%)
Steroid	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Vitrectomy	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Other	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Received Anti-VEGF, Steroid, or Vitrectomy for Conditions Other Than DR or DME, N (%)	**3**	**(3%)**	**1**	**(2%)**	**2**	**(2%)**	**2**	**(3%)**

[a] One eye (without color-PPL and with FA-PPL) received topical steroid and Acular for presumed CME, and another eye (with color-PPL and without FA-PPL) received Bromfenac drops.

[b] Indications include central retinal vein occlusion, vitreous hemorrhage, neovascular age-related macular degeneration, and choroidal neovascularization secondary to age-related macular degeneration.

eTable 6. Initial event for eyes meeting the primary outcome

Events [a]	By Baseline Color-PPL				By Baseline FA-PPL			
	Color-PPL Absent		Color-PPL Present		FA-PPL Absent		FA-PPL Present	
No. of Eyes	**323**		**221**		**295**		**247**	
No. of Eyes Meeting the Primary Outcome, N (%)	**111**	**(100%)**	**71**	**(100%)**	**71**	**(100%)**	**111**	**(100%)**
Two or more step DRSS worsening	97	(87%)	65	(92%)	57	(80%)	105	(95%)
Receipt of DR treatment	14	(13%)	6	(8%)	14	(20%)	6	(5%)
No. of Eyes Censored, N (%)	**212**	**(100%)**	**150**	**(100%)**	**224**	**(100%)**	**136**	**(100%)**
Completed study[b]	118	(56%)	104	(69%)	127	(57%)	95	(70%)
Received non-DR treatment	22	(10%)	5	(3%)	24	(11%)	2	(1%)
Lost to follow-up	72	(34%)	41	(27%)	73	(33%)	39	(29%)

[a] Defined as the initial event that categorized whether an eye met the primary outcome or was being censored.

[b] Eyes that completed 4-year follow-up without meeting the primary outcome or receiving non-DR treatment were censored at the 4-year visit.

eTable 7. Sensitivity Analyses of Primary Outcome: DRSS worsening by 2 or more steps within the ETDRS fields on masked UWF-color images or receipt of DR treatment through 4 years by Color-PPL

Competing-risk Analysis [a]		
	Cumulative Incidence Estimates (95% CI)	**Hazard Ratio (95% CI) from Subdistribution Hazard Model**
Outcome Event: ≥2-step DRSS worsening on masked UWF-color images or receipt of DR treatment		
By Baseline Color-PPL		
PPL Absent	41% (35%, 46%)	- Reference -
PPL Present	37% (30%, 44%)	0.81 (0.60, 1.11) *P* = .19
By Baseline DRSS Level		
Mild NPDR (Level 35)	45% (37%, 53%)	
Moderate NPDR (Level 43)	39% (31%, 48%)	
Moderately Severe NPDR (Level 47)	24% (15%, 35%)	
Severe and Very Severe NPDR (Level 53)	40% (31%, 49%)	
Competing Event: Receipt of non-DR treatment (for DME or other conditions)		
By Baseline Color-PPL		
PPL Absent	7.8% (5.1%, 11%)	- Reference -
PPL Present	2.6% (1.0%, 5.5%)	0.42 (0.16, 1.13) *P* = .08
By Baseline DRSS Level		
Mild NPDR (Level 35)	1.3% (0.3%, 4.3%)	
Moderate NPDR (Level 43)	5.3% (2.4%, 10%)	
Moderately Severe NPDR (Level 47)	9.7% (4.2%, 18%)	
Severe and Very Severe NPDR (Level 53)	9.0% (4.8%, 15%)	
Combined Outcome: ≥2-step DRSS worsening on masked UWF-color images or receipt of treatment for any conditions [b]		
	Kaplan-Meier Estimates (95% CI)	**Hazard Ratio (95% CI) from Cox Proportional Hazards Model**
By Baseline Color-PPL		
PPL Absent	48% (43%, 55%)	- Reference -
PPL Present	39% (33%, 47%)	0.73 (0.54, 0.98) *P* = .04
By Baseline DRSS Level		
Mild NPDR (Level 35)	46% (38%, 55%)	
Moderate NPDR (Level 43)	45% (36%, 54%)	
Moderately Severe NPDR (Level 47)	34% (24%, 46%)	
Severe and Very Severe NPDR (Level 53)	49% (41%, 59%)	
Inverse Probability Weighted Analysis [c]		
		Hazard Ratio (95% CI) from IPW Cox Model
By Baseline Color-PPL		
PPL Absent		- Reference -
PPL Present		0.92 (0.67, 1.28) *P* = .64

[a] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR were treated as experiencing a competing event. Eyes lost to follow-up or completing the visit without experiencing an outcome event (either ≥2-step DRSS worsening or DR treatment) or a competing event were censored at the last completed visit. The Fine-Gray subdistribution hazard model was adjusted for baseline ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant.

[b] The Cox proportional hazards model was adjusted for baseline ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant. Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for any conditions (including DR or DME treatment) were considered an outcome event.

[c] The IPW Cox model was adjusted for the correlation between the two study eyes from the same participant, weighted by the product of an estimated time-fixed inverse probability PPL weight and an estimated time-varying inverse probability censoring weight for each eye at each time point. Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for DR were considered an outcome event. The time-fixed PPL weight was derived from a logistic regression model with baseline color-PPL status as the dependent variable and potential baseline confounders (including age, diabetes type, diabetes duration, HbA1c, estimated glomerular filtration rate, albumin creatinine ratio, and DRSS level on masked UWF-color images) as the independent variables. Potential baseline confounders for the primary outcomes were selected based on a criterion of ≥10% difference in the Kaplan-Meier estimates between groups as shown in eTable 6 in Silva et al 2022 [Submitted]. The time-varying inverse probability censoring weight was obtained from a pooled logistic regression model with censoring as the dependent variable and color-PPL, time and baseline variables associated with censoring (including diabetes type, body mass index, insulin use, smoking, metformin use, estimated glomerular filtration rate, albumin creatinine ratio, and DRSS level on masked UWF-color images; eTable 9) as the independent variables. Baseline risk factors for censoring were selected based on a criterion of ≥10% difference in censoring between groups.

eTable 8. Sensitivity Analyses of Primary Outcome: DRSS worsening by 2 or more steps within the ETDRS fields on masked UWF-color images or receipt of DR treatment through 4 years by FA-PPL

Competing-risk Analysis [a]		
	Cumulative Incidence Estimates (95% CI)	**Hazard Ratio (95% CI) from Subdistribution Hazard Model**
Outcome Event: ≥2-step worsening on masked UWF-color images or receipt of DR treatment		
By Baseline FA-PPL		
FA-PPL Absent	29% (24%, 35%)	- Reference -
FA-PPL Present	50% (43%, 56%)	1.72 (1.25, 2.36) *P* <.001
Competing Event: Receipt of non-DR treatment (for DME or other conditions)		
By Baseline FA-PPL		
FA-PPL Absent	9.7% (6.4%, 14%)	- Reference -
FA-PPL Present	0.9% (0.2%, 2.9%)	0.10 (0.02, 0.47) *P* = .003
Combined Outcome: ≥2-step worsening on masked UWF-color images or receipt of treatment for any conditions [b]		
	Kaplan-Meier Estimates (95% CI)	**Hazard Ratio (95% CI) from Cox Proportional Hazards Model**
By Baseline FA-PPL		
FA-PPL Absent	39% (33%, 46%)	- Reference -
FA-PPL Present	51% (44%, 57%)	1.34 (1.00, 1.78) *P* = .05
Inverse Probability Weighted Analysis [c]		
		Hazard Ratio (95% CI) from IPW Cox Proportional Hazards Model
By Baseline FA-PPL		
FA-PPL Absent		- Reference -
FA-PPL Present		2.10 (1.50, 2.95) *P* < .001

[a] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR were treated as experiencing a competing event. Eyes lost to follow-up or completing the visit without experiencing an outcome event (either ≥2-step DRSS worsening or DR treatment) or a competing event were censored at the last completed visit. The Fine-Gray subdistribution hazard model was adjusted for baseline ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant.

[b] The Cox proportional hazards model was adjusted for ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant. Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for any conditions (including DR or DME treatment) were considered an outcome event.

[c] The IPW Cox model was adjusted for the correlation between the two study eyes from the same participant, weighted by the product of an estimated time-fixed inverse probability PPL weight and an estimated time-varying inverse probability censoring weight for each eye at each time point. Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for DR were considered an outcome event. The time-fixed PPL weight was derived from a logistic regression model with baseline FA-PPL status as the dependent variable and potential baseline confounders (including age, diabetes type, diabetes duration, HbA1c, estimated glomerular filtration rate, albumin creatinine ratio, and DRSS level on masked UWF-color images) as the independent variables. Potential baseline confounders for the primary outcomes were selected based on a criterion of ≥10% difference in the Kaplan-Meier estimates between groups as shown in eTable 6 in Silva et al 2022 [Submitted]. The time-varying inverse probability censoring weight was obtained from a pooled logistic regression model with censoring as the dependent variable and color-PPL, time and baseline variables associated with censoring (including diabetes type, body mass index, insulin use, smoking, metformin use, estimated glomerular filtration rate, albumin creatinine ratio, and DRSS level on masked UWF-color images; eTable 9) as the independent variables. Baseline risk factors for censoring were selected based on a criterion of ≥10% difference in censoring between groups.

eTable 9. Receipt of Treatment for Non-DR Conditions or Lost to Follow-up by Baseline Characteristics

	Total	Received Non-DR Treatment or Lost to Follow-up	
No. of Eyes, N (%)	544	140	(26%)
Participant Characteristics			
Gender			
Female	264	73	(28%)
Male	280	67	(24%)
Age (years)			
<60	227	58	(26%)
≥60	317	82	(26%)
Race/Ethnicity, N (%) [a]			
White	373	87	(23%)
Non-white	165	52	(32%)
Diabetes Type, N (%) [b]			
Type 1	82	11	(13%)
Type 2	456	125	(27%)
Duration of Diabetes (years)			
<20	259	76	(29%)
≥20	285	64	(22%)
Body Mass Index (%)			
<30	200	52	(26%)
≥30	303	70	(23%)
Unknown	41	18	(44%)
Hemoglobin A_{1c} (%) [c]			
<8.0	264	59	(22%)
≥8.0	273	79	(29%)
Insulin Used			
No	142	48	(34%)
Yes	402	92	(23%)
Smoking Status			
Current	54	19	(35%)
Never	346	85	(25%)
Prior	144	36	(25%)
Mean Arterial Pressure (mmHg)			
<97	265	71	(27%)
≥97	279	69	(25%)
History of Hypertension			
No	125	35	(28%)
Yes	419	105	(25%)
History of High Cholesterol/Dyslipidemia			
No	172	39	(23%)
Yes	372	101	(27%)
Taking Fenofibrate at Baseline			
No	522	131	(25%)
Yes	22	9	(41%)
Taking Metformin at Baseline			
No	280	70	(25%)

	Total	Received Non-DR Treatment or Lost to Follow-up	
No. of Eyes, N (%)	544	140	(26%)
Yes	246	60	(24%)
Unknown	18	10	(56%)
EGFR (mL/min/1.73 m^2)			
< 60	66	21	(32%)
≥ 60	249	50	(20%)
Unknown	229	69	(30%)
Albumin Creatinine Ratio			
No albuminuria (<30)	179	33	(18%)
Albuminuria (30-300)	133	40	(30%)
Unknown	232	67	(29%)
Number of Study Eyes			
1	190	52	(27%)
2	354	88	(25%)
Study Eye Characteristics			
Visual Acuity Letter Score			
< 84 (20/25 or worse)	204	62	(30%)
≥ 84 (20/20 or better)	340	78	(23%)
DRSS Level on UWF Masked Color Image by Reading Center Assessment			
Mild NPDR (Level 35)	172	35	(20%)
Moderate NPDR (Level 43)	149	35	(23%)
Moderately Severe NPDR (Level 47)	79	23	(29%)
Severe and Very Severe NPDR (Level 53)	144	47	(33%)
OCT CST Spectralis Equivalent (µm) [d]			
< 210	258	71	(28%)
≥ 210	286	69	(24%)
OCT Volume (mm^2) [e]			
< 7.0	289	64	(22%)
≥ 7.0	255	76	(30%)
Lens Status			
Aphakic or PC IOL	135	32	(24%)
Phakic	409	108	(26%)
History of DME Treatment			
No	425	117	(28%)
Yes	119	23	(19%)

[a] Excluding 6 eyes with unknown race/ethnicity

[b] Excluding 6 eyes with uncertain type

[c] Excluding 7 eyes with unavailable hbA1c

[d] Cirrus measurements were converted to Spectralis equivalents using the following formula: Spectralis = 40.78 + 0.95 × Cirrus.

[e] Retinal volume measurements were converted to Stratus equivalents using the following formulae: Stratus = -1.21 + 1.02 × Cirrus; Stratus = -2.05 + 1.06 × Spectralis.

eTable 10. Primary Outcome: DR worsening by 2 or more steps within the ETDRS fields on UWF-color images or receipt of DR treatment through 4 years by baseline DRSS level and PPL characteristics

Primary Outcome [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
By Baseline DRSS Level				
DRSS level within the ETDRS fields on UWF-color images				
Mild NPDR (Level 35)	172	45% (37%, 54%)	--	--
Moderate NPDR (Level 43)	149	40% (32%, 49%)	--	
Moderately Severe NPDR (Level 47)	79	26% (17%, 38%)	--	
Severe and Very Severe NPDR (Level 53)	144	43% (34%, 53%)	--	
Baseline Color-PPL Risk Factors				
Primary: Color-PPL Status				
PPL Absent	323	43% (37%, 49%)	- Reference -	.13
PPL Present	221	38% (31%, 45%)	0.78 (0.57, 1.08)	
Color-PPL Status for H/Ma				
PPL Absent	361	42% (36%, 48%)	- Reference -	--
PPL Present	180	37% (30%, 46%)	0.80 (0.56, 1.13)	
Color-PPL Status for IRMA				
PPL Absent	448	40% (35%, 46%)	- Reference -	--
PPL Present	84	35% (25%, 47%)	0.81 (0.54, 1.22)	
Color-PPL Status for VB				
PPL Absent	533	40% (36%, 45%)	--	--
PPL Present	5	40% (12%, 87%)	--	
Color-PPL Status for NVE				
PPL Absent	536	40% (36%, 45%)	--	--
PPL Present	8	57% (27%, 90%)	--	
Number of peripheral fields with Color-PPL				
No PPL	323	43% (37%, 49%)	Per unit increase in number of fields:	--
PPL in 1 Field	118	39% (30%, 49%)	0.88 (0.75, 1.03)	
PPL in ≥2 Fields	103	36% (27%, 47%)		
Color-PPL Status in Field 3				
PPL Absent	448	42% (37%, 47%)	- Reference -	--
PPL Present	89	35% (25%, 47%)	0.72 (0.47, 1.10)	
Color-PPL Status in Field 4				
PPL Absent	442	42% (37%, 47%)	- Reference -	--
PPL Present	93	32% (23%, 43%)	0.65 (0.43, 1.00)	
Color-PPL Status in Field 5				
PPL Absent	453	40% (35%, 45%)	- Reference -	--
PPL Present	74	39% (28%, 52%)	0.88 (0.55, 1.38)	
Color-PPL Status in Field 6				
PPL Absent	450	41% (36%, 46%)	- Reference -	--
PPL Present	85	37% (27%, 49%)	0.82 (0.54, 1.25)	
Color-PPL Status in Field 7				
PPL Absent	440	40% (35%, 45%)	- Reference -	--
PPL Present	58	40% (27%, 55%)	0.98 (0.61, 1.59)	
Baseline FA-PPL Risk Factors				
Primary: FA-PPL Status				
PPL Absent	295	31% (25%, 38%)	- Reference -	<.001
PPL Present	247	50% (44%, 57%)	1.72 (1.25, 2.36)	
FA-PPL Status for H/Ma				
PPL Absent	317	33% (28%, 40%)	- Reference -	.02

Primary Outcome [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
PPL Present	225	49% (42%, 56%)	1.47 (1.08, 2.01)	
FA-PPL Status for IRMA				
PPL Absent	430	37% (33%, 43%)	- Reference -	.04
PPL Present	112	51% (41%, 61%)	1.39 (1.02, 1.90)	
FA-PPL Status for VB				
PPL Absent	538	40% (36%, 45%)	--	--
PPL Present	4	67% (23%, 99%)	--	
FA-PPL Status for NVE				
PPL Absent	512	40% (35%, 45%)	- Reference -	.07
PPL Present	30	54% (37%, 72%)	1.68 (0.97, 2.91)	
Number of peripheral fields with FA-PPL				
No PPL	295	31% (25%, 38%)	Per unit increase in number of fields:	.64
PPL in 1 Field	75	65% (54%, 76%)	1.02 (0.94, 1.11)	
PPL in ≥2 Fields	172	43% (35%, 51%)		
FA-PPL Status in Field 3				
PPL Absent	406	39% (34%, 45%)	- Reference -	.40
PPL Present	136	44% (36%, 53%)	1.15 (0.83, 1.60)	
FA-PPL Status in Field 4				
PPL Absent	386	40% (35%, 46%)	- Reference -	.51
PPL Present	156	41% (33%, 49%)	0.90 (0.65, 1.24)	
FA-PPL Status in Field 5				
PPL Absent	435	41% (36%, 46%)	- Reference -	.61
PPL Present	107	41% (31%, 51%)	0.91 (0.63, 1.31)	
FA-PPL Status in Field 6				
PPL Absent	379	37% (32%, 42%)	- Reference -	.07
PPL Present	163	48% (40%, 57%)	1.33 (0.97, 1.82)	
FA-PPL Status in Field 7				
PPL Absent	437	40% (35%, 45%)	- Reference -	.80
PPL Present	105	43% (33%, 54%)	1.05 (0.72, 1.52)	

[a] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR were censored after treatment initiation. The Cox proportional hazards analysis was conducted only if there were at least 20 eyes in each stratum for the risk factor. The model was adjusted for baseline ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant.

[b] *P* value was reported only if the analysis of primary PPL showed a significant effect (i.e., $P < 0.05$).

eTable 11. Secondary Outcome: Development of PDR within the ETDRS fields on masked UWF-color images or receipt of DR treatment through 4 years by baseline DRSS level and PPL characteristics

Risk Factors [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
By Baseline DRSS Level				
DRSS level within the ETDRS fields on UWF-color images				
Mild NPDR (Level 35)	172	10% (6.2%, 17%)	--	--
Moderate NPDR (Level 43)	149	16% (10%, 23%)	--	
Moderately Severe NPDR (Level 47)	79	26% (17%, 38%)	--	
Severe and Very Severe NPDR (Level 53)	144	43% (34%, 53%)	--	
By Baseline Color-PPL Characteristics				
Primary: Color-PPL Status				
PPL Absent	323	26% (21%, 32%)	- Reference -	.67
PPL Present	221	17% (12%, 23%)	0.90 (0.57, 1.44)	
Color-PPL Status for H/Ma				
PPL Absent	361	26% (21%, 31%)	- Reference -	--
PPL Present	180	16% (11%, 22%)	0.92 (0.54, 1.58)	
Color-PPL Status for IRMA				
PPL Absent	448	23% (19%, 28%)	- Reference -	--
PPL Present	84	17% (10%, 28%)	0.82 (0.45, 1.50)	
Color-PPL Status for VB				
PPL Absent	533	22% (18%, 26%)	--	--
PPL Present	5	40% (12%, 87%)	--	
Color-PPL Status for NVE				
PPL Absent	536	22% (18%, 26%)	--	--
PPL Present	8	57% (27%, 90%)	--	
Number of peripheral fields with Color-PPL				
No PPL	323	26% (21%, 32%)	Per unit increase in number of fields:	--
PPL in 1 Field	118	20% (13%, 29%)	0.91 (0.70, 1.18)	
PPL in ≥2 Fields	103	14% (7.9%, 23%)		
Color-PPL Status in Field 3				
PPL Absent	448	25% (21%, 30%)	- Reference -	--
PPL Present	89	11% (5.4%, 20%)	0.61 (0.29, 1.26)	
Color-PPL Status in Field 4				
PPL Absent	442	25% (21%, 30%)	- Reference -	--
PPL Present	93	11% (5.9%, 20%)	0.61 (0.30, 1.23)	
Color-PPL Status in Field 5				
PPL Absent	453	23% (19%, 28%)	- Reference -	--
PPL Present	74	17% (10%, 29%)	1.17 (0.58, 2.35)	
Color-PPL Status in Field 6				
PPL Absent	450	23% (19%, 28%)	- Reference -	--
PPL Present	85	17% (10%, 28%)	0.96 (0.52, 1.77)	
Color-PPL Status in Field 7				
PPL Absent	440	23% (19%, 28%)	- Reference -	--
PPL Present	58	18% (10%, 32%)	1.03 (0.50, 2.15)	
By Baseline FA-PPL Characteristics				

Risk Factors [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
Primary: FA-PPL Status				
PPL Absent	295	20% (15%, 26%)	- Reference -	.03
PPL Present	247	24% (19%, 31%)	1.60 (1.05, 2.45)	
FA-PPL Status for H/Ma				
PPL Absent	317	23% (18%, 29%)	- Reference -	.50
PPL Present	225	21% (16%, 27%)	1.16 (0.75, 1.79)	
FA-PPL Status for IRMA				
PPL Absent	430	22% (18%, 26%)	- Reference -	.27
PPL Present	112	24% (17%, 34%)	1.30 (0.82, 2.07)	
FA-PPL Status for VB				
PPL Absent	538	22% (18%, 26%)	--	--
PPL Present	4	67% (23%, 99%)	--	
FA-PPL Status for NVE				
PPL Absent	512	20% (17%, 25%)	- Reference -	<.001
PPL Present	30	47% (31%, 66%)	3.49 (2.08, 5.85)	
Number of peripheral fields with FA-PPL				
No PPL	295	20% (15%, 26%)	Per unit increase in number of fields:	.69
PPL in 1 Field	75	40% (30%, 53%)	0.97 (0.85, 1.11)	
PPL in ≥2 Fields	172	17% (12%, 24%)		
FA-PPL Status in Field 3				
PPL Absent	406	25% (20%, 30%)	- Reference -	.41
PPL Present	136	15% (10%, 23%)	0.80 (0.47, 1.36)	
FA-PPL Status in Field 4				
PPL Absent	386	25% (21%, 30%)	- Reference -	.35
PPL Present	156	15% (10%, 23%)	0.78 (0.46, 1.32)	
FA-PPL Status in Field 5				
PPL Absent	435	23% (19%, 28%)	- Reference -	.57
PPL Present	107	17% (11%, 27%)	0.85 (0.48, 1.49)	
FA-PPL Status in Field 6				
PPL Absent	379	23% (18%, 28%)	- Reference -	.35
PPL Present	163	21% (15%, 28%)	1.24 (0.79, 1.96)	
FA-PPL Status in Field 7				
PPL Absent	437	23% (19%, 27%)	- Reference -	.95
PPL Present	105	20% (13%, 30%)	0.98 (0.57, 1.68)	

[a] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR were censored after treatment initiation. The Cox proportional hazards analysis was conducted only if there were at least 20 eyes in each stratum for the risk factor. *P* values for secondary PPL characteristics were only presented when $P < 0.05$ for primary PPL. The Cox proportional hazards model was adjusted for baseline ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant.

[b] *P* value was reported only if the analysis of primary PPL showed a significant effect (i.e., $P < 0.05$).

eTable 12. Secondary Outcome: Development of vitreous hemorrhage within the ETDRS fields on masked UWF-color images or at clinical exam or receipt of DR treatment through 4 years by baseline DRSS level and PPL characteristics

Risk Factors [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
By Baseline DRSS Level				
DRSS level within the ETDRS fields on UWF-color images				
Mild NPDR (Level 35)	172	4.2% (1.9%, 9.2%)	--	--
Moderate NPDR (Level 43)	149	7.1% (3.7%, 13%)	--	
Moderately Severe NPDR (Level 47)	79	18% (10%, 29%)	--	
Severe and Very Severe NPDR (Level 53)	144	22% (15%, 31%)	--	
By Baseline Color-PPL Characteristics				
Primary: Color-PPL Status				
PPL Absent	323	12% (8.8%, 17%)	- Reference -	.45
PPL Present	221	10% (6.6%, 15%)	1.28 (0.67, 2.41)	
Color-PPL Status for H/Ma				
PPL Absent	361	12% (8.6%, 16%)	- Reference -	--
PPL Present	180	11% (6.6%, 17%)	1.56 (0.76, 3.23)	
Color-PPL Status for IRMA				
PPL Absent	448	12% (8.6%, 15%)	- Reference -	--
PPL Present	84	10% (4.9%, 20%)	1.01 (0.44, 2.32)	
Color-PPL Status for VB				
PPL Absent	533	11% (8.6%, 15%)	--	--
PPL Present	5	20% (3.1%, 80%)	--	
Color-PPL Status for NVE				
PPL Absent	536	11% (8.0%, 14%)	--	--
PPL Present	8	57% (27%, 90%)	--	
Number of peripheral fields with Color-PPL				
No PPL	323	12% (8.8%, 17%)	Per unit increase in number of fields	--
PPL in 1 Field	118	10% (5.5%, 18%)	1.16 (0.84, 1.59)	
PPL in ≥2 Fields	103	10% (5.5%, 19%)		
Color-PPL Status in Field 3				
PPL Absent	448	12% (9.1%, 16%)	- Reference -	--
PPL Present	89	8.0% (3.7%, 17%)	1.07 (0.43, 2.64)	
Color-PPL Status in Field 4				
PPL Absent	442	12% (9.4%, 16%)	- Reference -	--
PPL Present	93	7.5% (3.4%, 16%)	0.95 (0.38, 2.33)	
Color-PPL Status in Field 5				
PPL Absent	453	11% (7.9%, 14%)	- Reference -	--
PPL Present	74	13% (6.6%, 24%)	2.18 (0.90, 5.27)	
Color-PPL Status in Field 6				
PPL Absent	450	12% (8.9%, 16%)	- Reference -	--
PPL Present	85	10% (4.9%, 20%)	1.16 (0.51, 2.68)	
Color-PPL Status in Field 7				
PPL Absent	440	11% (8.4%, 15%)	- Reference -	--

Risk Factors [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
PPL Present	58	12% (5.7%, 25%)	1.58 (0.63, 3.99)	
By Baseline FA-PPL Characteristics				
Primary: FA-PPL Status				
PPL Absent	295	11% (7.6%, 16%)	- Reference -	.24
PPL Present	247	12% (7.9%, 17%)	1.43 (0.79, 2.59)	
FA-PPL Status for H/Ma				
PPL Absent	317	13% (9.3%, 18%)	- Reference -	--
PPL Present	225	9.3% (5.9%, 14%)	0.96 (0.49, 1.89)	
FA-PPL Status for IRMA				
PPL Absent	430	11% (7.7%, 14%)	- Reference -	--
PPL Present	112	14% (8.5%, 23%)	1.70 (0.88, 3.28)	
FA-PPL Status for VB				
PPL Absent	538	11% (8.3%, 14%)	--	--
PPL Present	4	67% (23%, 99%)	--	
FA-PPL Status for NVE				
PPL Absent	512	9.8% (7.3%, 13%)	- Reference -	--
PPL Present	30	34% (20%, 54%)	4.95 (2.52, 9.71)	
Number of peripheral fields with FA-PPL				
No PPL	295	11% (7.6%, 16%)	Per unit increase in number of fields:	--
PPL in 1 Field	75	20% (12%, 31%)	0.97 (0.79, 1.19)	
PPL in ≥2 Fields	172	7.5% (4.2%, 13%)		
FA-PPL Status in Field 3				
PPL Absent	406	13% (9.6%, 17%)	- Reference -	--
PPL Present	136	7.4% (3.9%, 14%)	0.79 (0.35, 1.79)	
FA-PPL Status in Field 4				
PPL Absent	386	13% (10%, 18%)	- Reference -	--
PPL Present	156	6.6% (3.5%, 12%)	0.68 (0.30, 1.52)	
FA-PPL Status in Field 5				
PPL Absent	435	12% (9.3%, 16%)	- Reference -	--
PPL Present	107	7.6% (3.7%, 15%)	0.76 (0.31, 1.88)	
FA-PPL Status in Field 6				
PPL Absent	379	11% (7.8%, 15%)	- Reference -	--
PPL Present	163	12% (7.8%, 19%)	1.60 (0.85, 3.00)	
FA-PPL Status in Field 7				
PPL Absent	437	12% (9.0%, 16%)	- Reference -	--
PPL Present	105	8.6% (4.2%, 17%)	0.80 (0.33, 1.91)	

[a] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR were censored after treatment initiation. The Cox proportional hazards analysis was conducted only if there were at least 20 eyes in each stratum for the risk factor. *P* values for secondary PPL characteristics were only presented when $P < 0.05$ for primary PPL. The Cox proportional hazards model was adjusted for baseline ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant.

[b] *P* value was reported only if the analysis of primary PPL showed a significant effect (i.e., $P < 0.05$).

eTable 13. Secondary Outcome: DRSS improvement by 2 or more steps within the ETDRS fields on masked UWF-color images through 4 years by baseline DRSS level and PPL characteristics

Risk Factors [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
Overall Cohort by Baseline DRSS Level				
DRSS level within the ETDRS fields on UWF-color images				
Mild NPDR (Level 35)	172	2.9% (1.1%, 7.6%)	--	--
Moderate NPDR (Level 43)	149	1.0% (0.1%, 6.8%)	--	
Moderately Severe NPDR (Level 47)	79	27% (17%, 41%)	--	
Severe and Very Severe NPDR (Level 53)	144	53% (43%, 64%)	--	
Overall Cohort by Color-PPL				
Primary: Color-PPL Status				
PPL Absent	323	21% (16%, 27%)	--	--
PPL Present	221	13% (9.1%, 19%)	--	
By Baseline Color-PPL Characteristics [b] (Moderately Severe to Very Severe NPDR Only)				
Primary: Color-PPL Status				
PPL Absent	165	39% (31%, 49%)	- Reference -	.12
PPL Present	58	56% (40%, 74%)	1.44 (0.91, 2.28)	
Color-PPL Status for H/Ma				
PPL Absent	186	39% (31%, 48%)	- Reference -	--
PPL Present	37	70% (47%, 89%)	2.19 (1.30, 3.70)	
Color-PPL Status for IRMA				
PPL Absent	196	42% (34%, 50%)	- Reference -	--
PPL Present	27	60% (37%, 83%)	1.36 (0.75, 2.47)	
Color-PPL Status for VB				
PPL Absent	219	44% (36%, 52%)	--	--
PPL Present	4	25% (3.9%, 87%)	--	
Color-PPL Status for NVE				
PPL Absent	219	43% (36%, 52%)	--	--
PPL Present	4	33% (5.5%, 95%)	--	
Number of peripheral fields with Color-PPL				
No PPL	165	39% (31%, 49%)	Per unit increase in number of fields:	--
PPL in 1 Field	40	54% (34%, 75%)	1.31 (0.96, 1.79)	
PPL in ≥2 Fields	18	53% (31%, 79%)		
Color-PPL Status in Field 3				
PPL Absent	208	43% (36%, 52%)	--	--
PPL Present	14	55% (23%, 91%)	--	
Color-PPL Status in Field 4				
PPL Absent	204	42% (34%, 51%)	--	--
PPL Present	18	56% (31%, 84%)	--	
Color-PPL Status in Field 5				
PPL Absent	209	41% (34%, 50%)	--	--
PPL Present	12	79% (43%, 99%)	--	
Color-PPL Status in Field 6				
PPL Absent	200	43% (35%, 52%)	- Reference -	--

Risk Factors [a]	No. of Eyes	Kaplan-Meier Estimates (95% CI)	Hazard Ratio (95% CI)	*P* Value [b]
PPL Present	22	48% (27%, 74%)	1.46 (0.74, 2.89)	
Color-PPL Status in Field 7				
PPL Absent	194	41% (33%, 50%)	--	--
PPL Present	16	66% (33%, 95%)	--	
Overall Cohort by FA-PPL				
Primary: FA-PPL Status				
PPL Absent	295	17% (13%, 23%)	--	--
PPL Present	247	18% (13%, 24%)	--	
By Baseline FA-PPL Characteristics [c] (Moderately Severe to very Severe NPDR Only)				
Primary FA-PPL Status				
PPL Absent	148	33% (25%, 44%)	- Reference -	.02
PPL Present	74	65% (50%, 79%)	1.75 (1.11, 2.76)	
FA-PPL Status for H/Ma				
PPL Absent	160	32% (24%, 42%)	- Reference -	<.001
PPL Present	62	72% (57%, 86%)	2.23 (1.42, 3.52)	
FA-PPL Status for IRMA				
PPL Absent	190	40% (32%, 50%)	- Reference -	.15
PPL Present	32	62% (41%, 82%)	1.45 (0.88, 2.40)	
FA-PPL Status for VB				
PPL Absent	219	44% (36%, 52%)	--	--
PPL Present	3	0.0% (0.0%, 0.0%)	--	
FA-PPL Status for NVE				
PPL Absent	211	44% (36%, 52%)	--	--
PPL Present	11	39% (13%, 83%)	--	
Number of peripheral fields with FA-PPL				
No PPL	148	33% (25%, 44%)	Per unit increase in number of fields:	<.001
PPL in 1 Field	32	42% (22%, 71%)	1.26 (1.11, 1.44)	
PPL in ≥2 Fields	42	78% (61%, 91%)		
FA-PPL Status in Field 3				
PPL Absent	191	38% (30%, 47%)	- Reference -	.004
PPL Present	31	72% (53%, 88%)	2.01 (1.25, 3.22)	
FA-PPL Status in Field 4				
PPL Absent	186	36% (28%, 45%)	- Reference -	<.001
PPL Present	36	79% (62%, 93%)	2.90 (1.85, 4.56)	
FA-PPL Status in Field 5				
PPL Absent	195	36% (29%, 45%)	- Reference -	<.001
PPL Present	27	82% (62%, 95%)	2.38 (1.50, 3.78)	
FA-PPL Status in Field 6				
PPL Absent	178	42% (34%, 51%)	- Reference -	.74
PPL Present	44	57% (36%, 80%)	1.10 (0.64, 1.87)	
FA-PPL Status in Field 7				
PPL Absent	194	39% (31%, 48%)	- Reference -	.007
PPL Present	28	75% (52%, 93%)	1.98 (1.20, 3.26)	

[a] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for any conditions (including DR or DME) were censored after treatment initiation. The Cox proportional hazards analysis was conducted only if there were at least 20 eyes in each stratum for the risk factor. *P* values for secondary PPL characteristics were only presented when $P < 0.05$ for primary PPL. The Cox proportional hazards model was adjusted for baseline ETDRS-DRSS level within the ETDRS fields on UWF-color images and the correlation between the two study eyes from the same participant. At 4 years, only 8% (25 of 314) of eyes experienced 2 or more step DRSS improvement from baseline without initiating any treatment (<1% in mild NPDR, 0 in moderate NPDR, 11% in moderately severe NPDR and 31% in severe and very severe NPDR).

[b] *P* value was reported only if the analysis of primary PPL showed a significant effect (i.e., $P < 0.05$).

[c] Due to significant interaction between DRSS level and PPL ($P < .001$) and the low outcome rates in the mild and moderate NPDR subgroups, the analyses were limited to eyes with moderate severe or severe and very severe NPDR

eTable 14. Exploratory Outcomes by Primary PPL Characteristics on UWF-Color and UWF-FA Images

Outcomes	No. of Eyes	Kaplan-Meier Estimates (95% CI)
By Baseline Primary Color-PPL		
Worsening of 3 or more steps within the ETDRS fields on UWF-color images or receipt of DR treatment [a]		
Color-PPL Absent	323	26% (21%, 32%)
Color-PPL Present	221	18% (13%, 25%)
Worsening of 1 or more steps within the ETDRS fields on UWF-color images or receipt of DR treatment [a]		
Color-PPL Absent	323	65% (59%, 71%)
Color-PPL Present	221	54% (47%, 61%)
Receipt of DR treatment [a]		
Color-PPL Absent	323	12% (8.5%, 17%)
Color-PPL Present	221	9.0% (5.7%, 14%)
Development of vitreous hemorrhage within the ETDRS fields on UWF-color images or at clinical exam [b]		
Color-PPL Absent	323	3.2% (1.6%, 6.3%)
Color-PPL Present	221	4.8% (2.5%, 9.0%)
Improvement of 3 or more steps within the ETDRS fields on UWF-color images [b,c]		
Color-PPL Absent	240	13% (8.4%, 19%)
Color-PPL Present	132	10% (5.5%, 18%)
Improvement of 1 or more steps within the ETDRS fields on UWF-color images [b]		
Color-PPL Absent	323	49% (43%, 56%)
Color-PPL Present	221	42% (35%, 50%)
By Baseline Primary FA-PPL		
Worsening of 3 or more steps within the ETDRS fields on UWF-color images or receipt of DR treatment [a]		
FA-PPL Absent	295	19% (14%, 25%)
FA-PPL Present	247	27% (21%, 33%)
Worsening of 1 or more steps within the ETDRS fields on UWF-color images or receipt of DR treatment [a]		
FA-PPL Absent	295	56% (50%, 63%)
FA-PPL Present	247	64% (58%, 71%)
Receipt of DR treatment [a]		
FA-PPL Absent	295	11% (7.2%, 16%)
FA-PPL Present	247	11% (7.1%, 15%)
Development of vitreous hemorrhage within the ETDRS fields on UWF-color images or at clinical exam [b]		
FA-PPL Absent	295	3.1% (1.5%, 6.5%)
FA-PPL Present	247	4.6% (2.5%, 8.4%)
Improvement of 3 or more steps within the ETDRS fields on UWF-color images [b,c]		
FA-PPL Absent	228	8.4% (4.8%, 14%)
FA-PPL Present	143	16% (11%, 25%)
Improvement of 1 or more steps within the ETDRS fields on UWF-color images [b]		
FA-PPL Absent	295	50% (43%, 57%)
FA-PPL Present	247	41% (35%, 49%)

[a] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for conditions other than DR were censored after treatment initiation.

[b] Eyes receiving treatment with anti-VEGF, steroid, or vitrectomy for any conditions (including DR or DME) were censored after treatment initiation.

[c] Excluding eyes with mild NPDR (Level 35) at baseline because they cannot improve 3 steps.