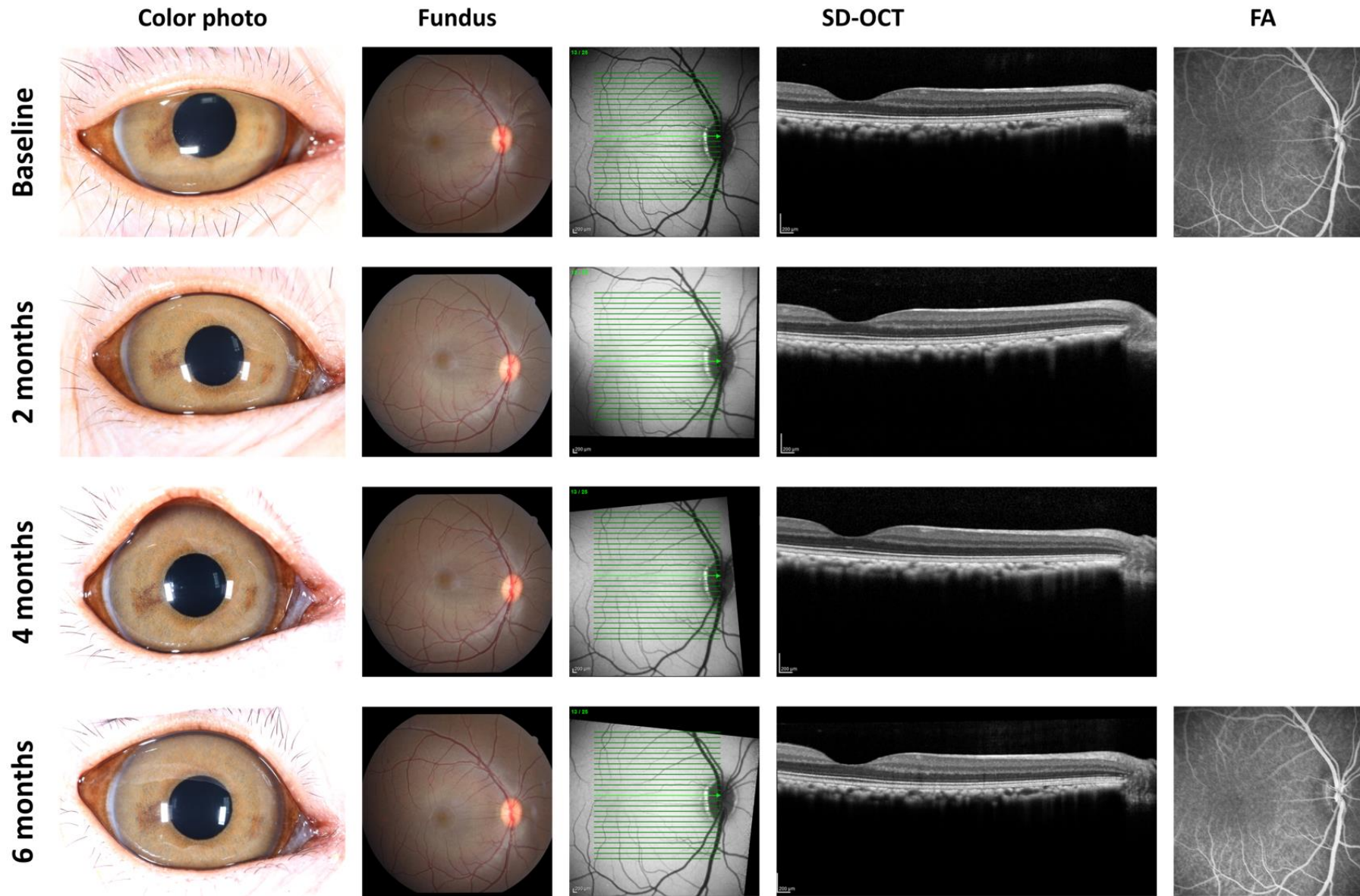


Suppl 1. Histopathology of a nonhuman primate who sustained a retinal tear at the time of IVT injection of aflibercept-DDS; vitreous hemorrhage was visible at 1 month post-injection (#7). (A) Gross photo demonstrates DDS material (*) in the superotemporal vitreous adjacent to pars planas. The DDS was opaque with well-defined borders and strings visible at 1 month post-IVT injection (A). (B) Dense accumulation of red blood cells was observed with clusters of macrophages in the anterior vitreous lining the pars plana and peripheral retina.

Suppl 2. Signalment, IVT injection and examination findings, and endpoints for the 10 nonhuman primates included in this study.

Animal #	Gender	Age (years)	Body weight (Kg)	DDS injection	Aqueous flare/cell (14-day post-inj.)	Aqueous flare/cell (at the end point)	Vitreous cell/floater (14-day post-inj.)	Vitreous cell/floater (at the end point)	Usage of the globes post euthanasia	End point (month post-inj.)
1	Male	8.5	13.41	Clear inj. at 6 times attempts	NA	0 / 0	NA	Tr / PB+TA	DDS concentration	1
2	Male	4.5	8.26	Clear inj. at once	NA	0 / 0	NA	2 / PW+TA	DDS concentration	2
3	Female	4.5	6.8	Clear inj. at 2 nd attempts	NA	0 / 0	NA	1 / PB+TA	DDS concentration	3
4	Female	5.2	6.25	Clear inj. at once	NA	0 / 0	NA	0 / TA	Lost sample	4
5	Female	7.5	8.65	Clear inj. at once	NA	0 / 0	NA	0 / TA	Lost sample	5
6	Male	6.3	7.6	Clear inj. at once	NA	0 / 0	NA	0 / TA	Lost sample	6
7	Female	11.7	9.75	5 times attempts: retinal hit and hemorrhage	Tr / 1	0 / 0	4 / PB+TA	2 / PW	Histopathology	1
8	Male	7.8	16.18	Clear inj. at 3 rd attempts	0 / 2 (PW)	0 / 0	2 / PB+TA	0 / TA	Histopathology	6
9	Female	11.5	7.15	Clear inj. at once	0 / 0	0 / 0	2 / M+TA	0 / TA	DDS concentration	6
10	Female	7.6	7.88	Clear inj. at once	0 / 0	0 / 0	1 / PB+TA	0 / TA	DDS concentration	5

Aqueous flare and vitreous cell were evaluated by the SPOTS system at 16X magnification and slit beam setting at 12 mm beam height, 0.2 mm beam width, with ~30-45° beam angle. 0 = ≤ 1, Tr (trace) = 1-5, 1 = 6-25, 2 = 26-50, 3 = 51-100, and 4 = > 100 cells in field; PW, predominantly white; M, mixed color; PB, predominantly brown; NA, not applicable; inj., injection; TA, test article.



Suppl 3. The funds and anterior structures appeared normal at all timepoint. Representative images of a 7.6 year old female rhesus macaque (#10) prior to injection (baseline) as well as 2, 4 and 6 months post-injection showed no morphological abnormalities or changes with anterior segment photography, fundus photography, blue auto-fluorescence (AF) with SD-OCT and fluorescein angiography (FA).

Suppl 4. Thickness of retinal layers measured by SD-OCT.

Retinal layers	Thickness	Group of eyes	Baseline	1 month	2 month	3 month	4 month	5 month	6 month
	P-values	ANOVA	Tukey's multiple comparisons test (between groups)						
Total retinal thickness (TRT)	thickness (µm)	Treatment (OD)	263.7 ± 6.8	269.7 ± 6.8	265.3 ± 6.8	272.0 ± 6.8	271.0 ± 6.8	268.7 ± 6.8	268.4 ± 7.0
		Control (OS)	260.7 ± 6.8	266.3 ± 7.0	267.4 ± 6.8	265.3 ± 6.8	265.7 ± 6.8	269.7 ± 6.8	271.9 ± 7.0
	P (between group)	0.65	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
	P (between time)	0.93	OD / OS	0.97 / 0.98	>0.99 / 0.96	0.89 / >0.99	0.94 / 0.99	0.99 / 0.86	>0.99 / 0.72
Nerve fiber layer (NFL)	thickness (µm)	Treatment (OD)	13.0 ± 1.3	12.3 ± 1.2	10.7 ± 1.3	13.0 ± 1.3	13.3 ± 1.3	11.3 ± 1.2	11.9 ± 1.4
		Control (OS)	13.7 ± 1.3	14.0 ± 1.4	12.3 ± 1.3	10.7 ± 1.2	10.7 ± 1.3	13.3 ± 1.3	11.4 ± 1.4
	P (between group)	0.92	>0.99	>0.99	>0.99	0.99	0.97	>0.99	>0.99
	P (between time)	0.70	OD / OS	>0.99 / >0.99	0.64 / 0.95	>0.99 / 0.40	>0.99 / 0.40	0.87 / >0.99	0.96 / 0.66
Ganglion cell/inner plexiform layers (GCL/IPL)	thickness (µm)	Treatment (OD)	32.0 ± 1.7	33.3 ± 1.8	33.7 ± 1.8	33.3 ± 1.7	33.0 ± 1.7	33.3 ± 1.8	34.3 ± 1.9
		Control (OS)	34.7 ± 1.8	35.6 ± 2.0	32.7 ± 1.8	32.3 ± 1.8	33.0 ± 1.7	34.0 ± 1.8	36.3 ± 2.0
	P (between group)	0.43	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
	P (between time)	0.83	OD / OS	0.99 / >0.99	0.97 / 0.93	0.99 / 0.88	>0.99 / 0.97	0.99 / >0.99	0.89 / 0.97
Inner nuclear layer (INL)	thickness (µm)	Treatment (OD)	21.3 ± 1.2	18.0 ± 1.2	18.0 ± 1.2	18.0 ± 1.2	18.3 ± 1.2	19.0 ± 1.2	19.2 ± 1.4
		Control (OS)	19.7 ± 1.2	17.1 ± 1.4	18.7 ± 1.2	16.7 ± 1.2	18.0 ± 1.2	18.3 ± 1.2	22.7 ± 1.4
	P (between group)	0.88	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	0.78
	P (between time)	0.05	OD / OS	0.28 / 0.53	0.28 / 0.98	0.28 / 0.38	0.38 / 0.86	0.62 / 0.94	0.71 / 0.36
Outer plexiform layer (OPL)	thickness (µm)	Treatment (OD)	23.0 ± 1.6	20.0 ± 1.6	22.7 ± 1.6	22.0 ± 1.7	22.3 ± 1.6	21.3 ± 1.6	22.4 ± 1.8
		Control (OS)	21.3 ± 1.6	24.3 ± 1.8	24.3 ± 1.6	25.7 ± 1.6	20.7 ± 1.7	22.7 ± 1.6	20.4 ± 1.7
	P (between group)	0.38	>0.99	0.85	>0.99	0.95	>0.99	>0.99	>0.99
	P (between time)	0.71	OD / OS	0.64 / 0.65	>0.99 / 0.64	>0.99 / 0.30	>0.99 / >0.99	0.95 / 0.98	>0.99 / >0.99
Outer nuclear layer (ONL)	thickness (µm)	Treatment (OD)	87.3 ± 2.7	92.7 ± 2.7	91.0 ± 2.0	90.0 ± 2.7	88.0 ± 2.6	91.0 ± 2.7	86.7 ± 2.9
		Control (OS)	89.7 ± 2.7	91.2 ± 2.9	91.0 ± 2.7	83.7 ± 2.7	89.3 ± 2.7	89.0 ± 2.7	88.2 ± 2.9
	P (between group)	0.61	>0.99	>0.99	>0.99	0.92	>0.99	>0.99	>0.99
	P (between time)	0.48	OD / OS	0.57 / >0.99	0.85 / >0.99	0.96 / 0.46	>0.99 / >0.99	0.75 / >0.99	>0.99 / >0.99
Retinal pigment epithelium (RPE)	thickness (µm)	Treatment (OD)	19.3 ± 1.9	23.3 ± 1.9	19.0 ± 1.9	22.7 ± 1.9	24.0 ± 1.9	18.7 ± 1.9	22.8 ± 2.3
		Control (OS)	16.7 ± 1.9	18.5 ± 2.3	21.0 ± 1.9	20.0 ± 1.9	23.7 ± 1.9	20.0 ± 1.9	23.7 ± 2.2
	P (between group)	0.41	>0.99	0.89	>0.99	>0.99	>0.99	>0.99	>0.99
	P (between time)	0.07	OD / OS	0.53 / 0.97	>0.99 / 0.45	0.70 / 0.70	0.36 / 0.08	>0.99 / 0.70	0.68 / 0.08
Inner retinal layer (IRL)	thickness (µm)	Treatment (OD)	173.0 ± 6.2	174.7 ± 6.1	174.0 ± 6.2	171.3 ± 6.2	171.7 ± 6.1	174.0 ± 6.2	170.4 ± 6.3
		Control (OS)	172.7 ± 6.2	179.8 ± 6.3	175.0 ± 6.2	165.7 ± 6.2	167.0 ± 6.2	174.3 ± 6.1	172.9 ± 6.3
	P (between group)	0.94	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
	P (between time)	0.81	OD / OS	>0.99 / 0.91	>0.99 / >0.99	>0.99 / 0.92	>0.99 / 0.97	>0.99 / >0.99	>0.99 / >0.99
Outer retinal layer (ORL)	thickness (µm)	Treatment (OD)	90.3 ± 2.2	95.0 ± 2.3	91.3 ± 2.2	100.7 ± 2.2	99.3 ± 2.1	95.0 ± 2.2	98.0 ± 2.7
		Control (OS)	88.0 ± 2.2	87.5 ± 2.7	92.0 ± 2.2	99.3 ± 2.2	99.3 ± 2.1	95.0 ± 2.2	99.5 ± 2.8
	P (between group)	0.31	>0.99	0.59	>0.99	>0.99	>0.99	>0.99	>0.99
	P (between time)	0.06	OD / OS	0.50 / 0.99	>0.99 / 0.82	0.05 / 0.08	0.09 / 0.05	0.50 / 0.31	0.16 / 0.05

Suppl 5. Rod and cone a- and b-wave amplitudes and implicit times as measured by full-field electroretinography.

ERG measurements		Amplitudes	Group of eyes	Baseline	1 month	2 month	3 month	4 month	5 month	6 month	
		P-values	ANOVA	Tukey's multiple comparisons test							
Scotopic (Dark adaptation)	a-wave	amplitude (μV)	Treatment (OD)	162.0 \pm 24.8	136.3 \pm 29.7	148.2 \pm 24.8	134.9 \pm 24.8	118.7 \pm 24.8	160.7 \pm 24.8	136.7 \pm 29.8	
			Control (OS)	118.3 \pm 24.8	103.9 \pm 24.8	118.0 \pm 24.8	116.8 \pm 24.8	149.3 \pm 24.8	143.3 \pm 24.8	153.7 \pm 29.8	
		P (between group)	0.34	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
		P (between time)	0.90	OD / OS	0.98 / >0.99	>0.99 / >0.99	0.98 / >0.99	0.82 / 0.96	>0.99 / 0.96	0.98 / 0.92	
		implicit time (ms)	Treatment (OD)	13.8 \pm 0.7	14.7 \pm 1.3	13.8 \pm 0.9	11.9 \pm 0.8	12.7 \pm 1.9	12.9 \pm 1.1	12.7 \pm 1.3	
			Control (OS)	13.8 \pm 1.2	14.7 \pm 2.2	12.0 \pm 1.3	12.9 \pm 2.1	11.6 \pm 1.4	12.9 \pm 0.9	12.7 \pm 1.4	
	P (between group)	0.72	>0.99	>0.99	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	
	P (between time)	0.58	OD / OS	>0.99 / >0.99	>0.99 / 0.87	0.84 / >0.99	0.98 / 0.75	>0.99 / >0.99	0.98 / 0.98		
	b-wave	amplitude (μV)	Treatment (OD)	295.0 \pm 50.5	238.5 \pm 55.9	278/4 \pm 56.0	242.7 \pm 50.5	241.7 \pm 50.5	253.7 \pm 50.5	217.4 \pm 56.0	
			Control (OS)	254.7 \pm 50.5	222.3 \pm 50.5	231.7 \pm 50.5	229.0 \pm 50.5	237.3 \pm 50.5	218.3 \pm 50.5	220.9 \pm 56.0	
		P (between group)	0.44	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	
		P (between time)	0.96	OD / OS	0.97 / >0.99	>0.99 / >0.99	0.96 / >0.99	0.98 / >0.99	>0.99 / >0.99	0.88 / >0.99	
implicit time (ms)		Treatment (OD)	44.6 \pm 2.5	41.4 \pm 0.4	36.9 \pm 3.7	44.4 \pm 8.3	41.3 \pm 1.1	41.5 \pm 3.8	42.1 \pm 4.5		
		Control (OS)	45.6 \pm 2.6	43.6 \pm 1.4	39.2 \pm 1.6	40.9 \pm 3.5	40.2 \pm 4.6	43.7 \pm 7.5	40.9 \pm 5.9		
P (between group)	0.91	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99		
P (between time)	0.80	OD / OS	0.99 / >0.99	0.65 / 0.79	>0.99 / 0.93	0.99 / 0.88	>0.99 / >0.99	>0.99 / 0.93			
Photopic (Light adaptation)	a-wave	amplitude (μV)	Treatment (OD)	18.0 \pm 5.3	19.9 \pm 5.3	11.2 \pm 6.2	13.5 \pm 5.3	13.3 \pm 5.3	17.5 \pm 5.3	22.4 \pm 6.2	
			Control (OS)	21.3 \pm 5.3	20.7 \pm 5.3	18.8 \pm 6.2	17.7 \pm 5.3	7.8 \pm 5.3	21.7 \pm 5.3	23.5 \pm 6.2	
		P (between group)	0.45	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	
		P (between time)	0.38	OD / OS	>0.99 / >0.99	0.89 / >0.99	0.98 / >0.99	0.98 / 0.36	>0.99 / >0.99	0.98 / >0.99	
		implicit time (ms)	Treatment (OD)	12.1 \pm 2.1	12.6 \pm 1.1	12.1 \pm 1.6	12.9 \pm 1.5	12.8 \pm 0.2	12.9 \pm 1.6	13.4 \pm 0.5	
			Control (OS)	13.6 \pm 1.1	15.0 \pm 3.8	13.3 \pm 0.3	13.2 \pm 1.3	10.9 \pm 1.3	13.1 \pm 0.7	13.4 \pm 0.3	
	P (between group)	0.52	>0.99	0.89	>0.99	>0.99	0.97	>0.99	>0.99	>0.99	
	P (between time)	0.92	OD / OS	>0.99 / 0.97	>0.99 / >0.99	>0.99 / >0.99	>0.99 / 0.64	>0.99 / >0.99	0.98 / >0.99		
	b-wave	amplitude (μV)	Treatment (OD)	74.1 \pm 17.3	68.4 \pm 17.3	80.0 \pm 18.1	61.0 \pm 17.3	69.4 \pm 17.3	95.1 \pm 17.3	72.6 \pm 18.1	
			Control (OS)	97.5 \pm 17.3	65.6 \pm 17.3	79.8 \pm 18.1	66.9 \pm 17.3	81.7 \pm 17.3	86.9 \pm 17.3	78.7 \pm 18.1	
		P (between group)	0.58	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	
		P (between time)	0.73	OD / OS	>0.99 / 0.62	>0.99 / 0.95	0.99 / 0.67	>0.99 / 0.97	0.90 / >0.99	>0.99 / 0.94	
implicit time (ms)		Treatment (OD)	30.1 \pm 1.9	27.6 \pm 1.2	28.0 \pm 0.4	28.4 \pm 2.8	28.0 \pm 3.1	28.0 \pm 1.9	27.0 \pm 1.8		
		Control (OS)	29.9 \pm 0.9	27.7 \pm 1.6	27.9 \pm 0.4	28.6 \pm 2.7	28.9 \pm 4.0	28.9 \pm 1.6	27.6 \pm 0.8		
P (between group)	0.76	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99		
P (between time)	0.90	OD / OS	0.90 / 0.94	0.95 / 0.96	0.98 / >0.99	0.95 / >0.99	0.95 / >0.99	0.78 / 0.92			