Phase 1 Study of Intravitreal Gene Therapy with ADVM-022 for Neovascular Age-related Macular Degeneration (OPTIC Trial Cohort 1 & 2)

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– On behalf of the OPTIC investigators –

OPTIC
Gene Therapy in nAMD

Angiogenesis, Exudation, and Degeneration 2020 • Miami, FL • February 8, 2020

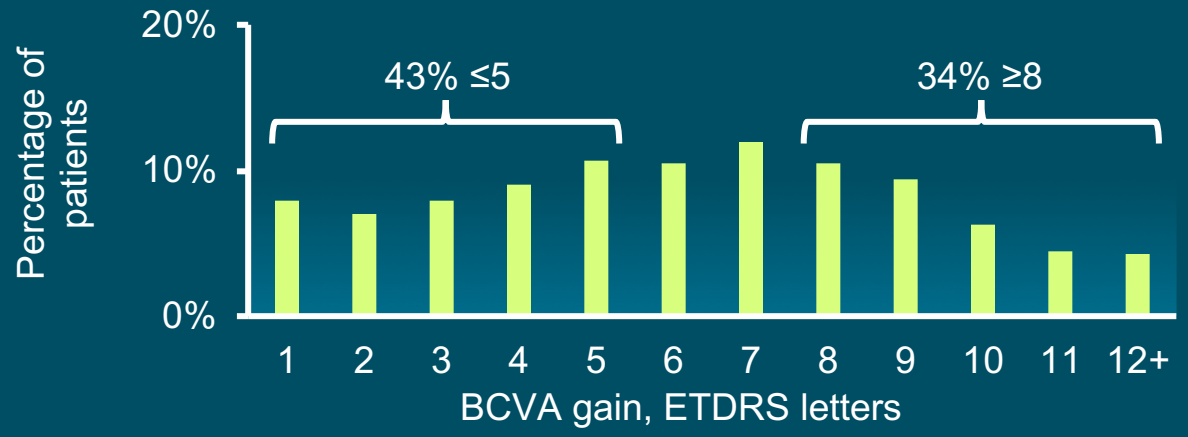
Disclosures

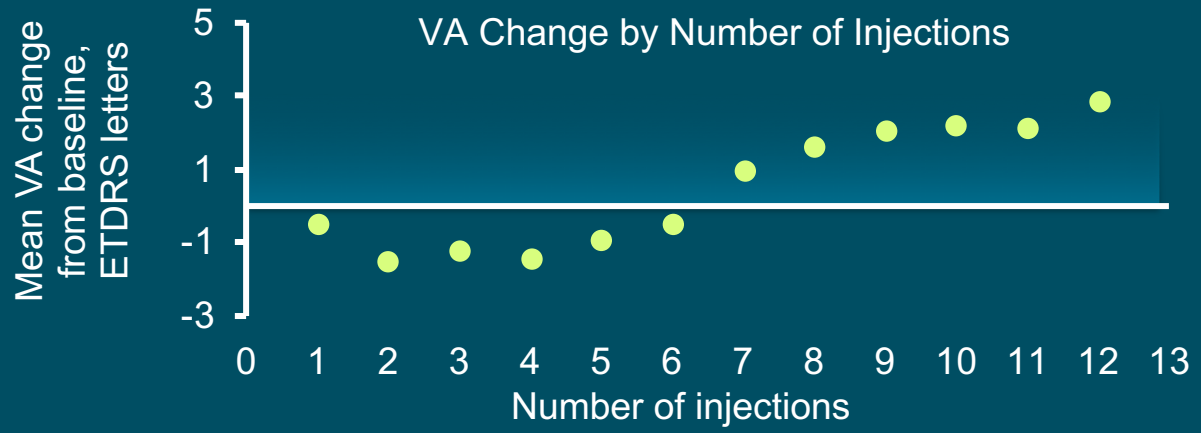
- Acuela (C); Adverum (C, R); Aerie Pharmaceuticals (R); Aerpio (C, R); Alimera Sciences (C); Allegro (C); Allergan (C, R); Apellis (C, R); Bayer (C); Chengdu Kanghong (C, R); Clearside Biomedical (C, R); EyePoint (C); Gemini Therapeutics (R); Genentech/Roche (C, R); Graybug Vision (R); IONIS Pharmaceuticals (R); Kodiak (C, R); Neurotech (R), Novartis (C, R); ONL Therapeutics (C); Opthea (R); Outlook Therapeutics (R); Oxurion (C); Recens Medical (C, R); Regeneron (C, R); Regenxbio (C, R); Roche (C,R); Santen (C, R); Takeda (C).

High Treatment Burden Associated with Frequent Injections

Injection Frequency for Optimal Outcomes Often Not Realized in Real-world

37,021 Eyes of 30,106 US Patients Receiving Routine Intravitreal Anti-VEGF Therapy Over 12 Months





Development Approach to Deliver Long-term Efficacy

Gene therapy

Establish an intraocular biofactory to produce an anti-VEGF agent

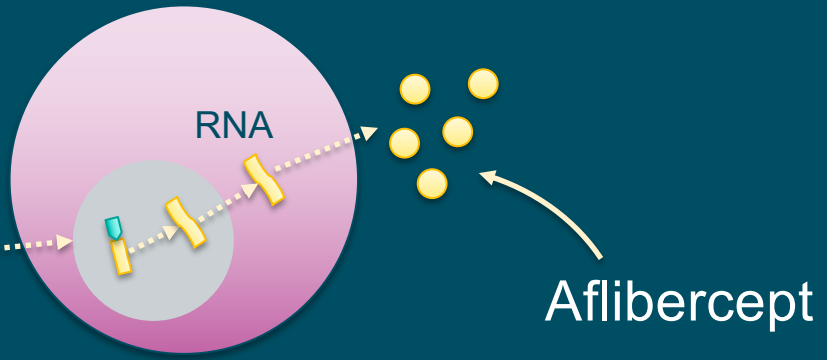
BCVA, best-corrected VA; ETDRS, Early Treatment Diabetic Retinopathy Study
VA, visual acuity; VEGF, vascular endothelial growth factor

ADVM-022: Adeno-Associated Virus Gene Therapy Vector Designed For Delivery by Intravitreal Injection

AAV.7m8 capsid

Capsid engineered from wild-type AAV2 by directed evolution and screened for highly efficient retinal transduction following IVT injection

Aflibercept expression cassette



Target retinal cell expresses aflibercept

Strong, ubiquitous promoter designed for robust protein expression

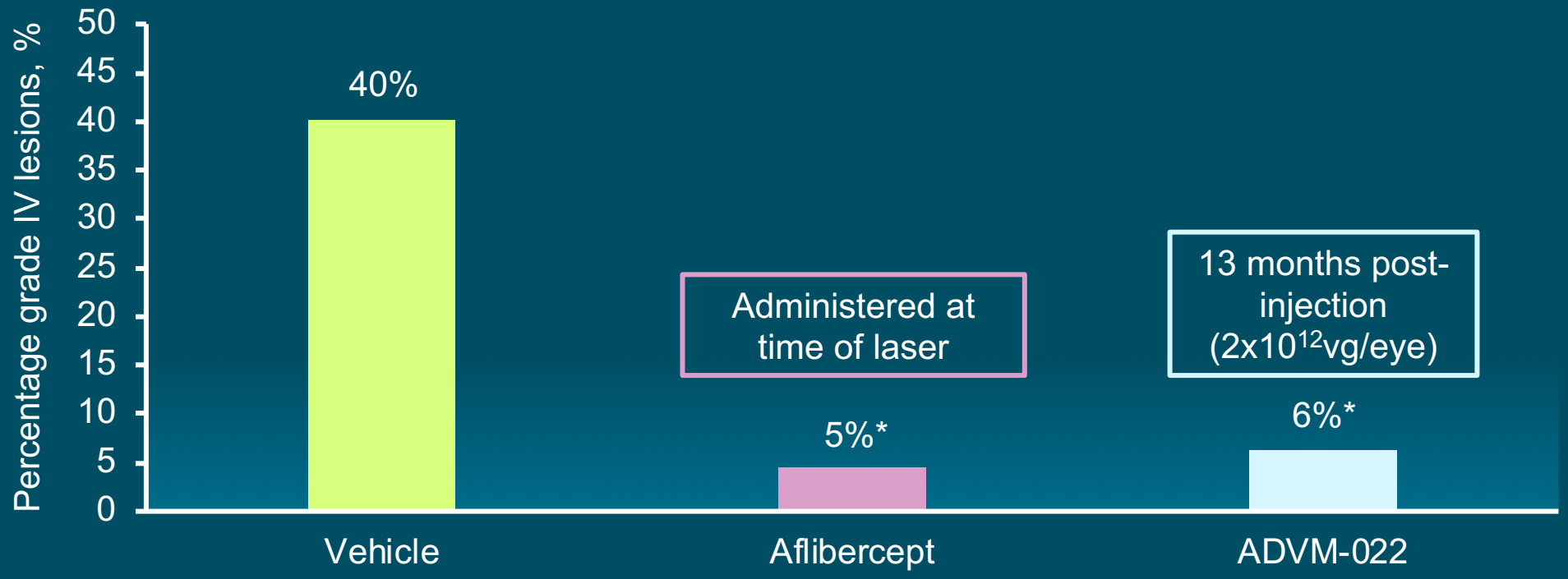
Codon-optimized cDNA

IVT, intravitreal

Grishanin, R et al. Mol Ther 2019;27:118–29

ADVM-022 Aflibercept is Functionally Active and Suppresses Laser-induced CNV in Primates

ADVM-022 given 13 months prior to laser-induced CNV is as effective as aflibercept administered at the time of laser



*p<0.0001(Fisher's exact test versus vehicle)
CNV, choroidal neovascularization

Grishanin, R et al. Mol Ther 2019;27:118–29

OPTIC: Phase 1, Two-year Multicenter Dose-ranging Study of ADVM-022 in Neovascular AMD

- Primary objective
  - Assess the safety and tolerability of a single IVT injection of ADVM-022
- Secondary objectives
  - Evaluate vision (BCVA)
  - Evaluate anatomy (SD-OCT)
  - Assess the need for rescue therapy

Oral steroid prophylaxis*: Cohort 1 ($6x10^{11}$vg/eye, n=6) and Cohort 2 ($2x10^{11}$vg/eye, n=6)

Steroid eye drops prophylaxis**: Cohort 3 ($2x10^{11}$vg/eye, n=9) and Cohort 4 ($6x10^{11}$vg/eye, n=9)

Patients receive rescue aflibercept (2mg IVT) if *any* of the following criteria are met:

1. Loss of ≥10 letters in BCVA from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

*Subjects received prophylaxis of 60mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper.
**Subjects receive prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.
BCVA, best-corrected visual acuity; IVT, intravitreal therapy; SD-OCT, spectral domain optical coherence tomography; QID, 4x/day

NCT03748784

Angiogenesis Cohort 1 & 2 Presentation

- Baseline characteristics
- Safety and treatment exposure
  - Through January 1, 2020
- Cohort 1 – $6x10^{11}$vg/eye dose
  - Through December 1, 2019
  - Cellular inflammation
  - OCT/BCVA outcomes
- Cohort 2 – $2x10^{11}$vg/eye dose
  - 24-week follow up
  - Cellular inflammation
  - OCT/BCVA outcomes

BCVA, best-corrected visual acuity; CST; central subfield thickness
OCT, optical coherence tomography; VEGF, vascular endothelial growth factor

Study Population Previously Required Frequent Injections to Maintain Vision

Baseline Characteristics	Cohort 1 (N=6)	Cohort 2 (N=6)
Mean age, years	79.0	79.8
Mean time since nAMD diagnosis, years	3.3	4.0
Mean (range) number anti-VEGF injections since initial diagnosis	35.3 (7–109)	34.0 (4–69)
Mean number anti-VEGF injections in 12 months prior to ADVM-022	9.2	9.2
Mean BCVA study eye, ETDRS letters Approximate Snellen equivalent	65.8 20/50	64.7 20/50
Mean CST study eye, µm	369.2	307.7

BCVA, best corrected visual acuity: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study
nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor

Cohort 1 & 2 Safety Summary through January 1, 2020

- No ADVM-022- or procedure-related serious adverse events (SAEs)
- No ADVM-022-related systemic adverse events
- No adverse events met criteria for dose-limiting toxicity
- ADVM-022-related adverse events have been mild (71%) to moderate (29%)
  - Low-grade inflammation commonly reported
  - No vasculitis, retinitis, or choroiditis
- One unrelated ocular SAE
  - Spontaneous, pseudophakic* retinal detachment
  - Surgically repaired and remains under follow-up

*Previous cataract extraction and artificial lens implantation

Cohort 1 – $6x10^{11}$vg/eye dose

OPTIC
Gene Therapy in nAMD

Cohort 1

As of December 1, 2019 (Median of 44 Weeks; Range 40–52 Weeks)

OPTIC Gene Therapy in AMD

Outcomes Through December 1, 2019 (Median 44 Weeks Follow-up)*	Value
Mean BCVA change from baseline, ETDRS letters	–1.0
BCVA change from baseline (min, max), ETDRS letters	–7, +7
Mean CST change from baseline, µm	–25.5
CST change from baseline (min, max), µm	–117, +32
Total number of rescue injections	0

*BCVA and CST for patient 4 with retinal detachment (unrelated to study treatment) use last observations prior to detachment (week 36)

BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study

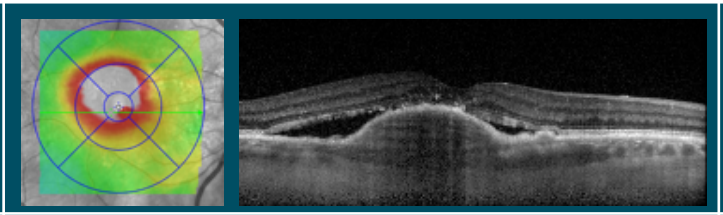
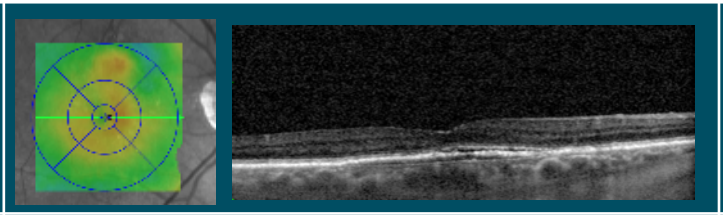
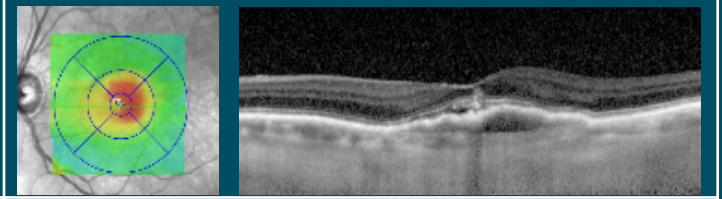
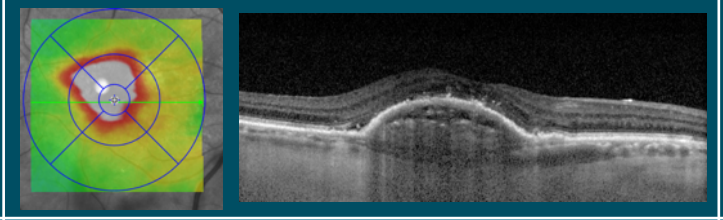
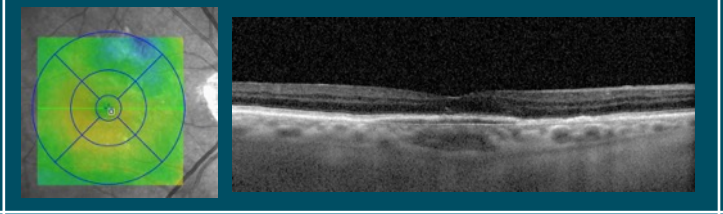
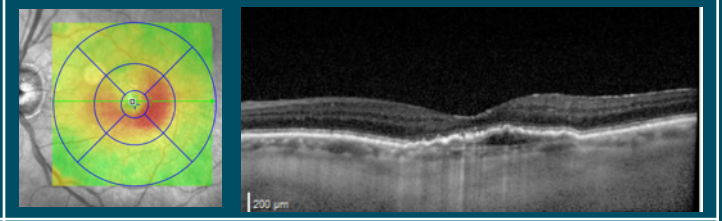
Cellular Inflammation Assessed by Slit Lamp Examination

Cohort 1: Low Grade and Responsive to Topical Steroids December 1, 2019

Aqueous cell grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria: Jabs DA, et al. J Ophthalmol 2005;140:509–516
Vitreous cell grade categories are based on National Institutes of Health (NIH) guidelines
Aqueous cells: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells
Vitreous cells: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; rare cells are captured as 0.5+ for this analysis

Individual Patient BCVA and OCT Outcomes

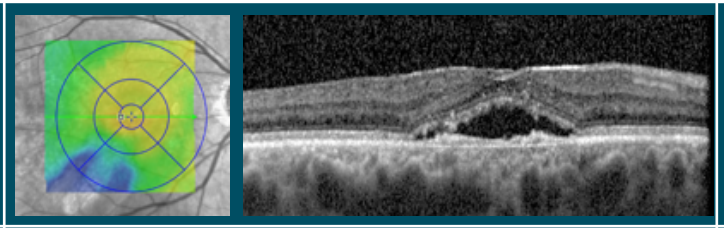
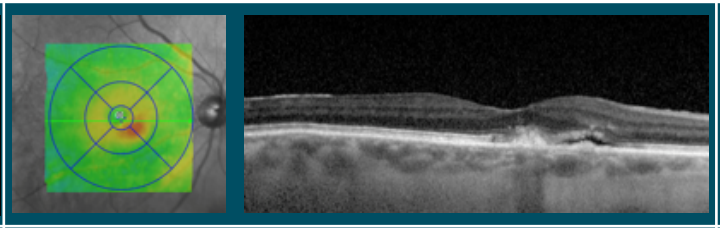
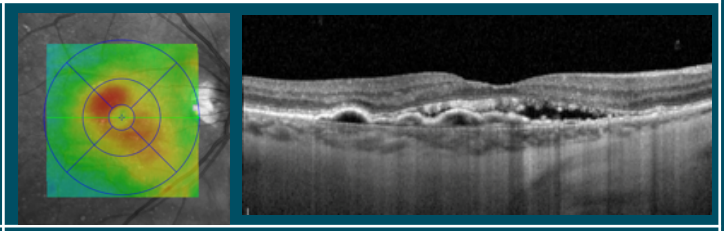
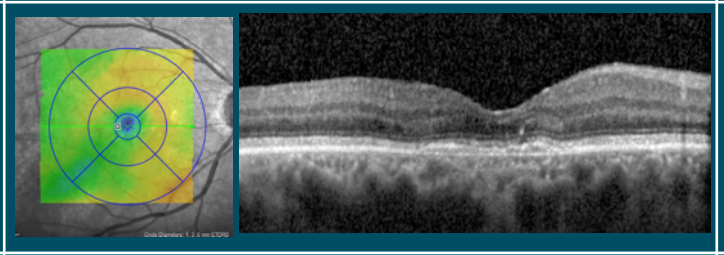
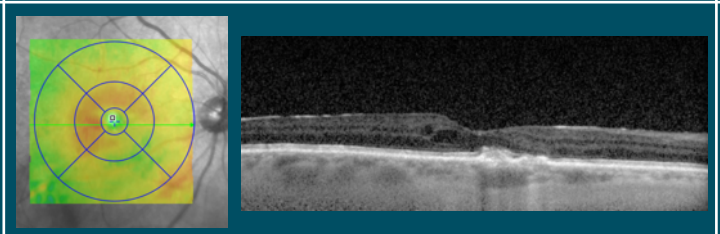
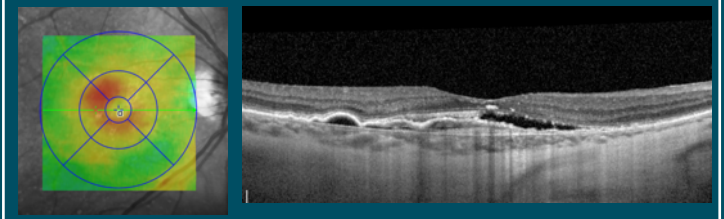
Cohort 1 – Follow-up Through December 1, 2019

	Patient 1: 52 Weeks Post-ADVM-022	Patient 2: 48 Weeks Post-ADVM-022	Patient 3: 44 Weeks Post-ADVM-022
Baseline OCT			
Latest OCT			
BCVA Change from Baseline, ETDRS letters	+7	–6	–7
CST change from Baseline, µm	+32	–29	–55
Rescue IVT in OPTIC, n	0	0	0

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study
IVT, intravitreal therapy; OCT, optical coherence tomography

Individual Patient BCVA and OCT Outcomes

Cohort 1 – Follow-up Through December 1, 2019

	Patient 4: 44 Weeks* Post-ADVM-022	Patient 5: 40 Weeks Post-ADVM-022	Patient 6: 40 Weeks Post-ADVM-022
Baseline OCT			
Latest OCT			
BCVA Change from Baseline, ETDRS letters	**+5***	**–2**	**–3**
CST change from Baseline, µm	**–117***	**+4**	**+12**
Rescue IVT in OPTIC, n	**0**	**0**	**0**

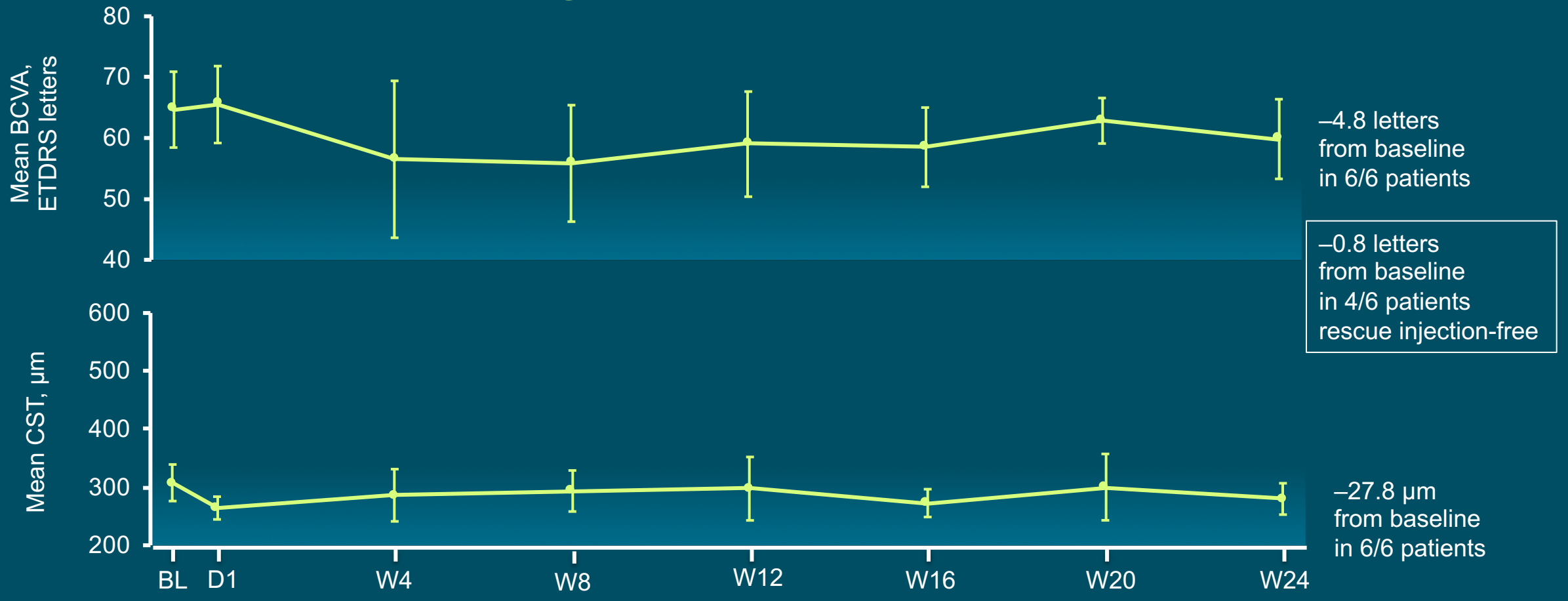
*BCVA, CST and OCT images for patient with retinal detachment (unrelated to study treatment) uses last observations prior to detachment (Week 36)

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography

Cohort 2 – $2x10^{11}$vg/eye dose

OPTIC
Gene Therapy in nAMD

Cohort 2: Mean BCVA and Mean CST Outcomes Through 24 Weeks



Aflibercept 2mg IVT administered at baseline, 7-15 days prior to ADVM-022 IVT (Day 1)

BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week

Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

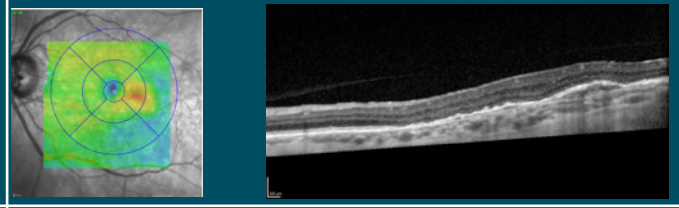
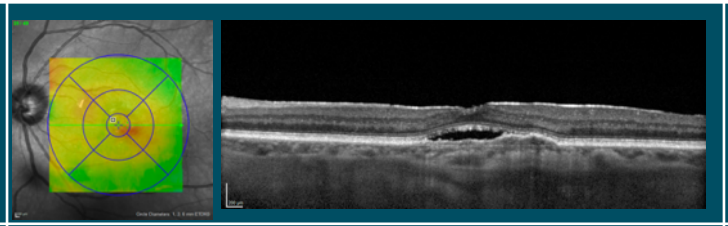
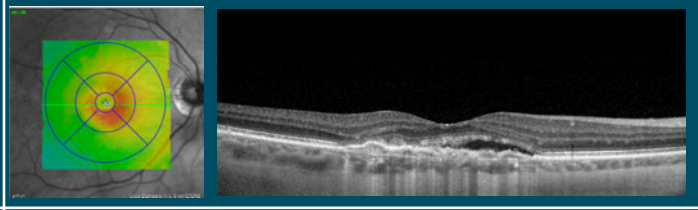
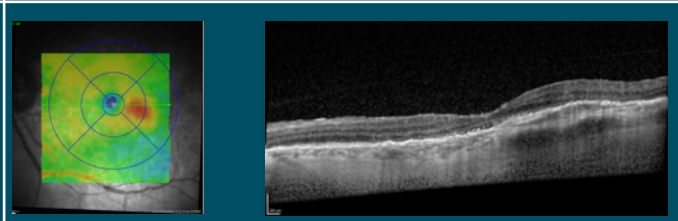
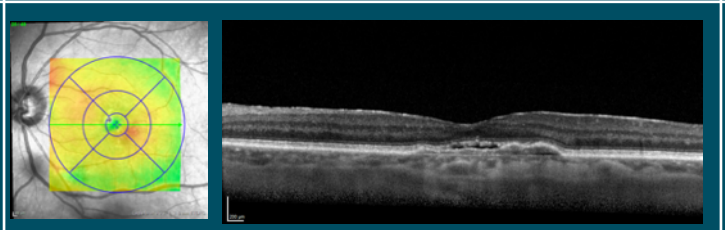
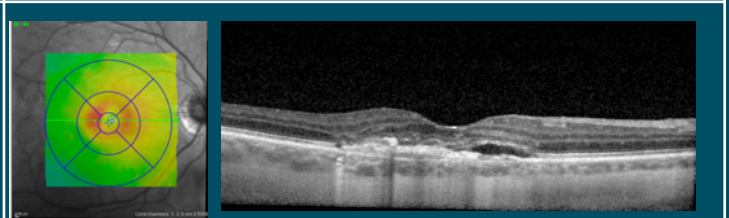
Cellular Inflammation Assessed by Slit Lamp Examination

Cohort 2: Inflammation Responsive to and Managed with Topical Steroids

Aqueous cell grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria: Jabs DA, et al. J Ophthalmol 2005;140:509–516
Vitreous cell grade categories are based on National Institutes of Health (NIH) guidelines
Aqueous cells: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells
Vitreous cells: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; rare cells are captured as 0.5+ for this analysis
Numbers within yellow bars represent frequency of difluprednate eye drops

Individual Patient BCVA and OCT Outcomes

Cohort 2 – 24 weeks

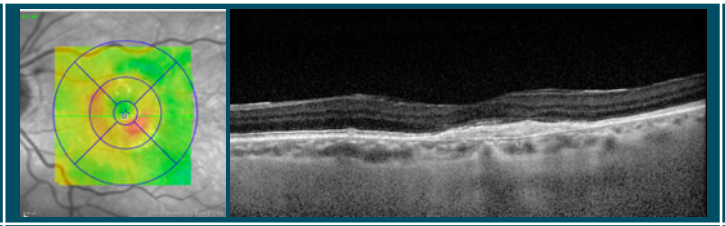
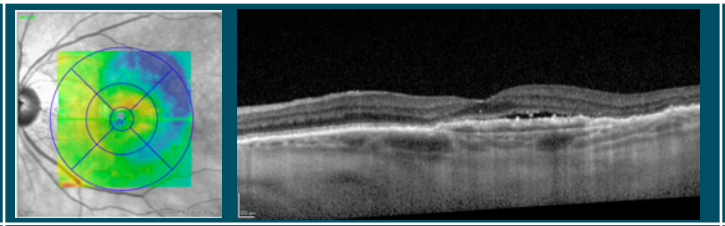
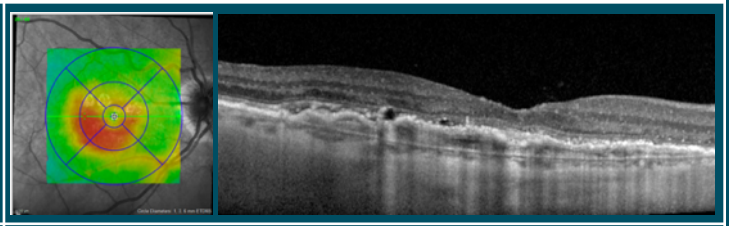
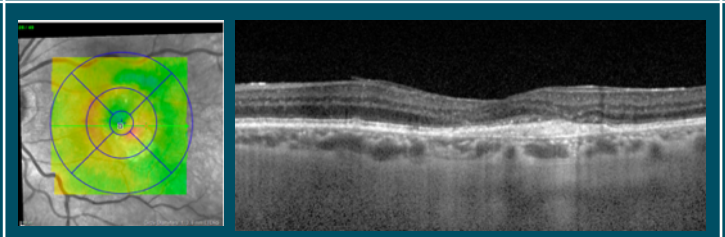
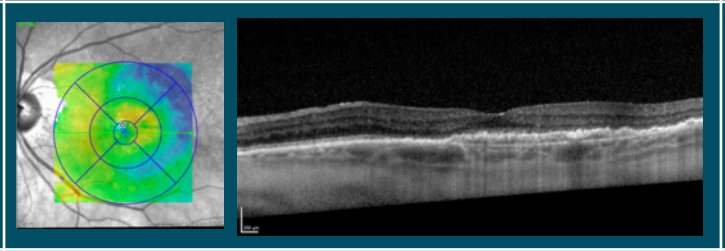
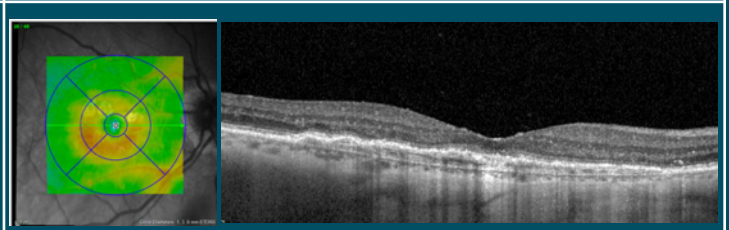
	Patient 1: 24 Weeks Post-ADVM-022	Patient 2: 24 Weeks Post-ADVM-022	Patient 3: 24 Weeks Post-ADVM-022
Baseline OCT			
Latest OCT			
BCVA Change from Baseline, ETDRS letters	**–4**	**–1**	**–19***
CST change from Baseline, µm	**–8**	**–38**	**–11***
Rescue IVT in OPTIC, n	**0**	**0**	**3***

*Patient 3 received rescue injection at week 24 due to loss of ≥10 letters in BCVA from baseline that is attributed to intraretinal or subretinal fluid

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study
IVT, intravitreal therapy; OCT, optical coherence tomography

Individual Patient BCVA and OCT Outcomes

Cohort 2 – 24 weeks

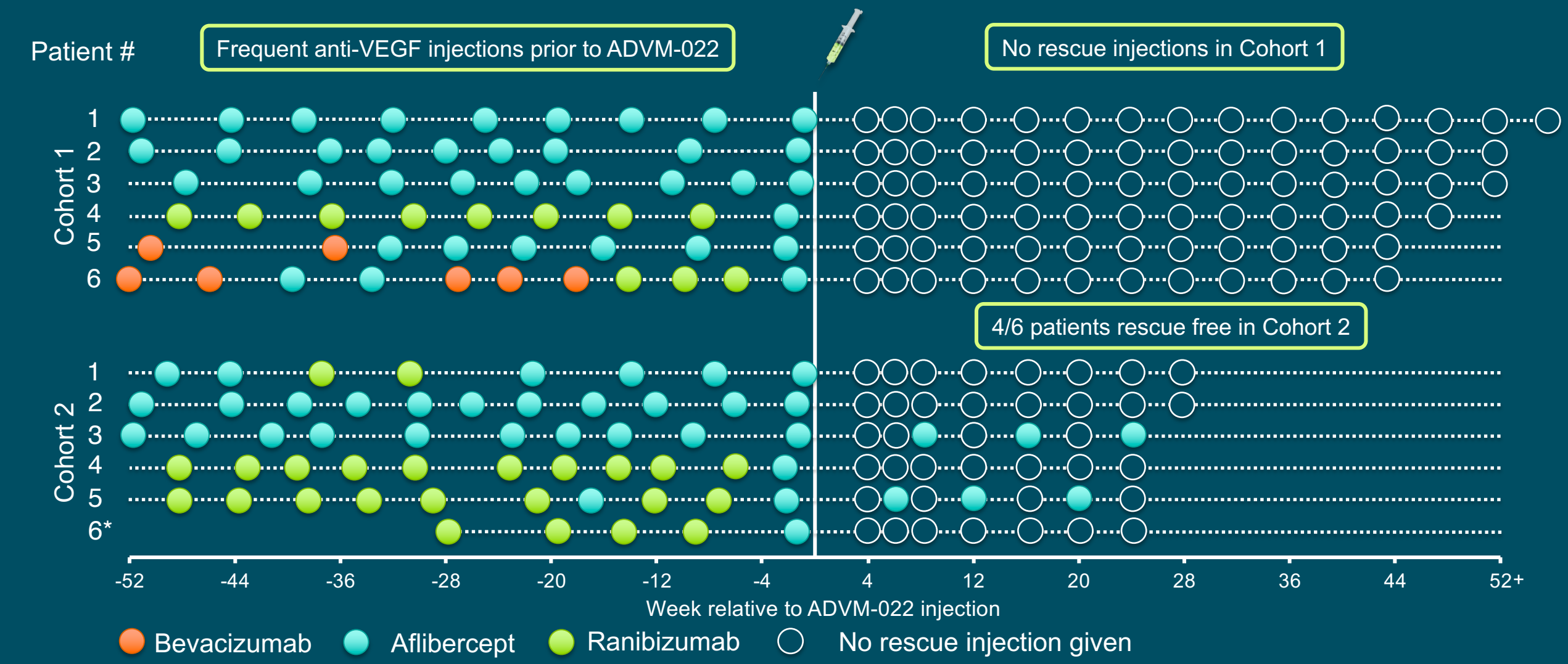
	Patient 4: 24 Weeks Post-ADVM-022	Patient 5: 24 Weeks Post-ADVM-022	Patient 6: 24 Weeks Post-ADVM-022
Baseline OCT			
Latest OCT			
BCVA Change from Baseline, ETDRS letters	–14	–7*	+16
CST change from Baseline, µm	–16	–33*	–61
Rescue IVT in OPTIC, n	0	3*	0

* Patient 5 received rescue injection at week 20 due to increase in central subfield thickness >75µm from baseline

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study
IVT, intravitreal therapy; OCT, optical coherence tomography

No Rescue Injections in Cohort 1, 4/6 Patients in Cohort 2 Remain Rescue Free

Follow-up Through January 1, 2020



*Patient 6 was diagnosed with nAMD 6.4 months prior to ADVM-022 injection date

OPTIC Cohort 1 & 2 Conclusions

- Robust efficacy signal with evidence of dose response:
  - $6x10^{11}$vg/eye: 6/6 patients rescue injection free
  - $2x10^{11}$vg/eye: 4/6 patients rescue injection free
- In 10 of 12 (83%) patients that were rescue injection free
  - Mean BCVA maintained
  - Mean CST improved
- Ocular inflammation responsive to steroid eyedrops
  - Cohorts 3 and 4 utilize 6-week prophylactic steroid eye drop regimen
- ADVM-022 demonstrates further potential to greatly reduce anti-VEGF injection burden in neovascular AMD

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor

ADVM-022 Acknowledgments

Investigators, study teams and participants

- David Boyer MD
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- Adam Turpcu, PhD