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

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– On behalf of the OPTIC investigators –

OPTIC
Gene Therapy in nAMD

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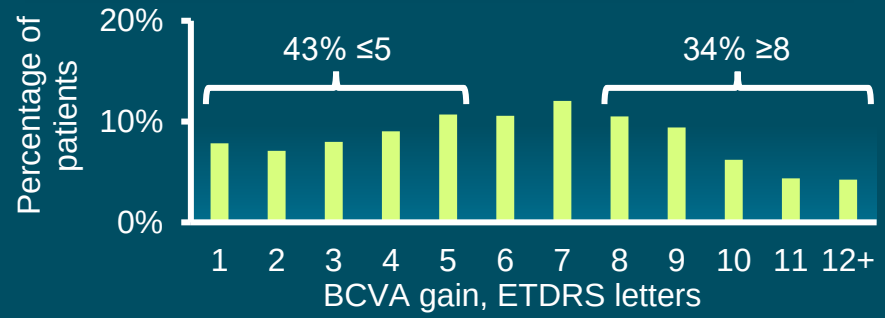
Disclosures

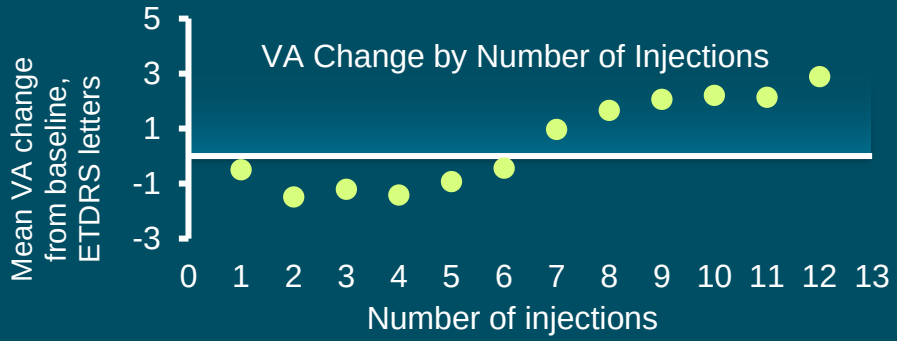
- CCW: Acuela (C); Adverum (C, R); Aerie Pharmaceuticals (R); Aerpio (C, R); Alimera Sciences (C); Allegro (C); Allergan (C, R); Apellis (C, R); Bayer (C); Chengdu Kanghong (C, R); Clearside Biomedical (C, R); DORC (C); EyePoint (C); Gemini Therapeutics (R); Genentech/Roche (C, R); Graybug Vision (R);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

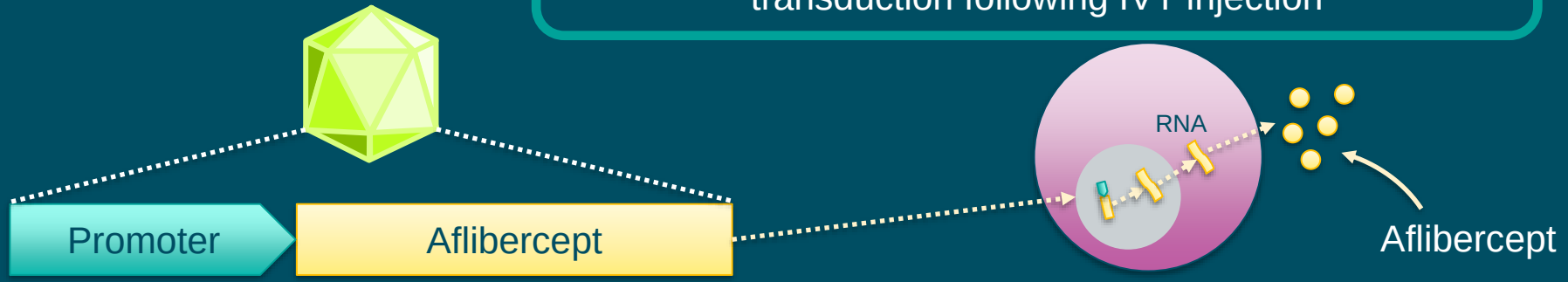
BCVA, best-corrected VA; ETDRS, Early Treatment Diabetic Retinopathy Study
VA, visual acuity; VEGF, vascular endothelial growth factor

Wykoff CC. Retina Society; Sept 13, 2018, San Francisco, CA

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

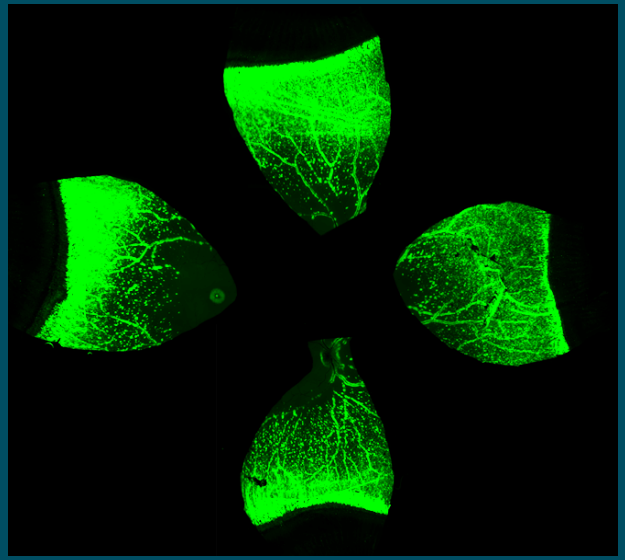
Codon-optimized cDNA

IVT, intravitreal

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

Intravitreal Injection of AAV.7m8 Results in Robust Cellular Transduction and Protein Expression in the Eye

- Advanced AAV.7m8 vector developed using directed evolution to:
  - enable efficient intravitreal delivery[1,3]
  - increase transduction of retinal cells[1,3]
  - increase protein expression[1]
- Protein expression in NHPs:
  - photoreceptors, ganglion cells[1–3]
  - bipolar cells, Müller cells, optic nerve[2]
  - ciliary epithelium, iris pigment epithelium[2]



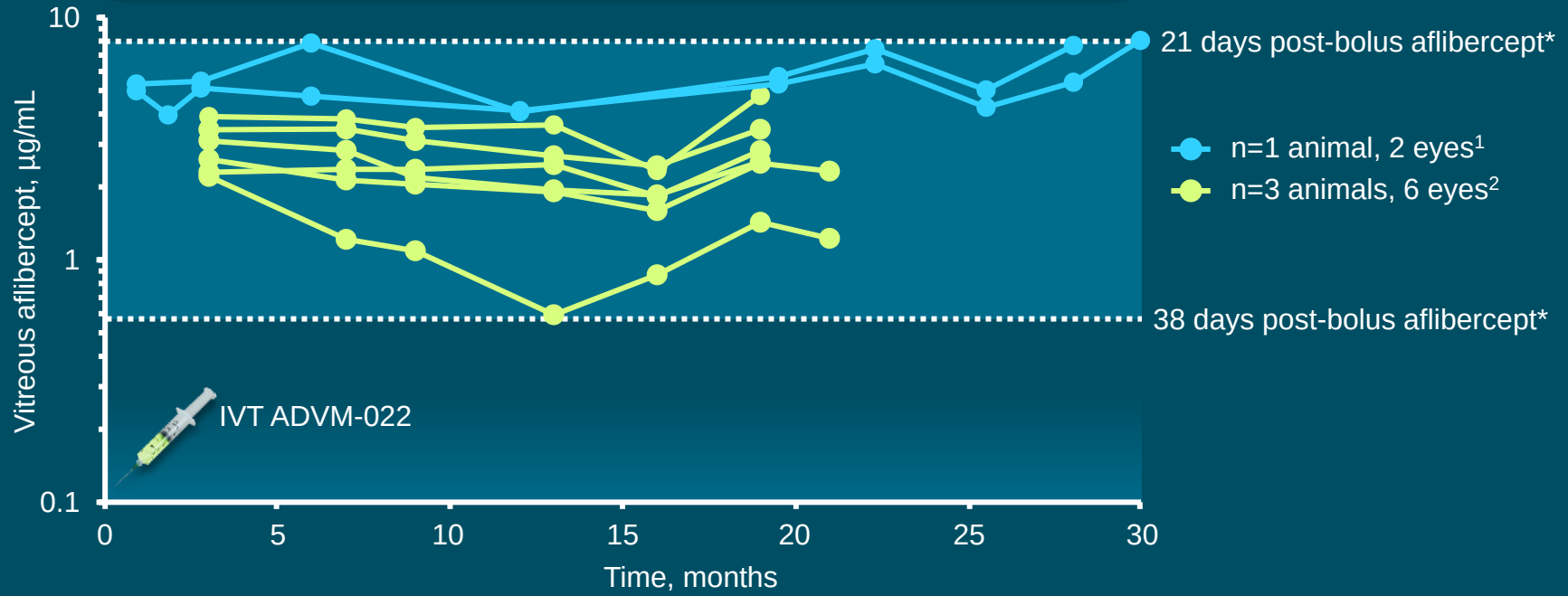
Green fluorescent protein expression in non-human primate retina[1]

1. Grishanin, R. et al. Mol. Ther. 2019;27:118–29
2. Ramachandran PS, et al. Hum Gene Ther 2017;28:154–67
3. Dalkara, D. et al. Sci Transl Med 2013, 5:189ra76

NHP, non-human primate

Preclinical NHP Data Demonstrate Long-Term Sustained Aflibercept Levels Comparable to Aflibercept Bolus Injection

Two studies: Stable long-term protein expression up to 21 and 30 months after single ADVM-022 IVT injection

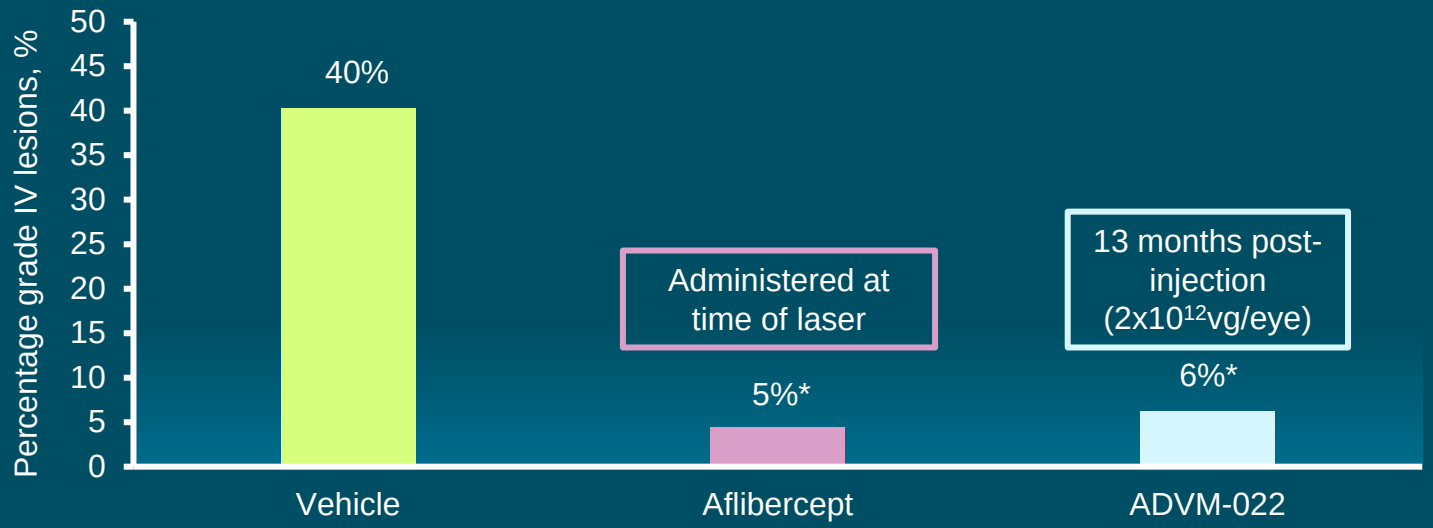


*Time after IVT injection of bolus aflibercept protein (1.2mg/eye; separate study) when similar aflibercept levels were observed in NHPs
NHP, non-human primate

1. Kiss, S. Ann Meeting of the Am Soc Gene Cell Ther; 2019, Washington, DC
2. Grishanin, R Ann Congress Eur Soc Gene Cell Ther; 2018, Lausanne, Switzerland

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

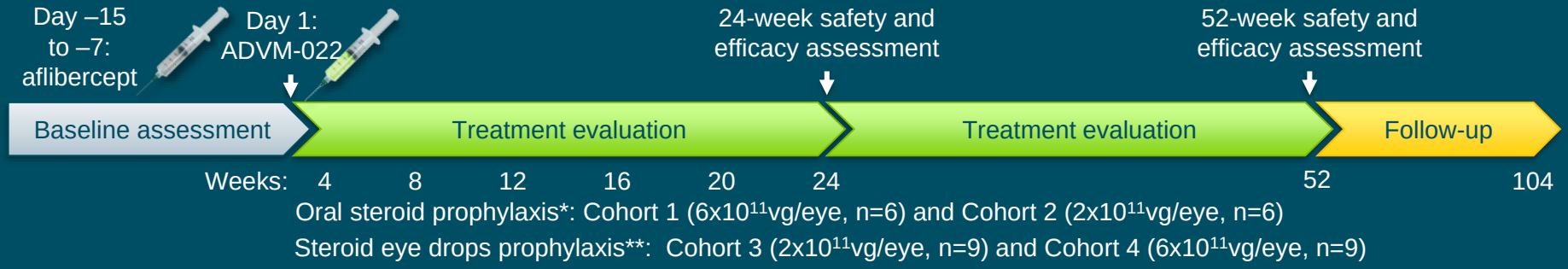


*p<0.0001(Fisher's exact test versus vehicle)
CNV, choroidal neovascularization

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

OPTIC: Phase 1, Two-year Multicenter 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

Study Population Previously Required Frequent Injections to Maintain Vision

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

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

December 1, 2019

Update of OPTIC Cohort 1

Data Through December 1, 2019 (n=6)	Value
Median follow-up, weeks	44.0
Follow-up (min, max), weeks	40, 52

Presentation includes:

- Safety
- Time-course and management of intraocular inflammation
- Mean change in BCVA and CST
- Individual patient OCTs/BCVA/CST at most recent visit
- Anti-VEGF rescue requirement

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

Cohort 1 Safety Results Through December 1, 2019

- 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 (75%) to moderate (25%)
  - 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

Cellular Inflammation Assessed by Slit Lamp Examination

Cohort 1: Low Grade and Responsive to 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

Cohort 1 Update: Additional Follow-up Data

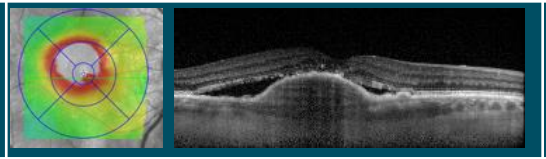
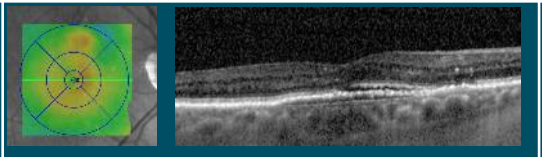
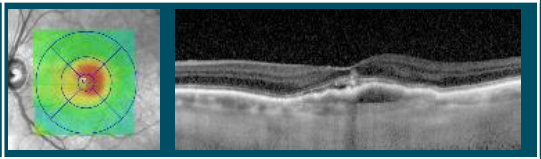
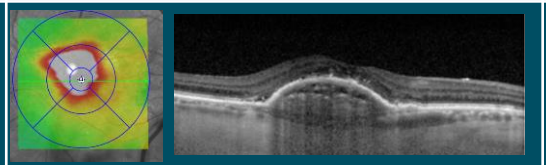
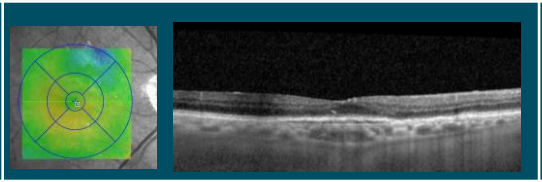
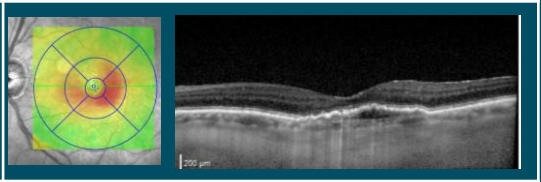
Outcomes Through December 1, 2019 (Median 44 Weeks Follow-up)*	Value
Mean BCVA change from baseline, ETDRS letters	–1.0
BCVA change from baseline (min, max), ETDRS letters	–7, +7
Mean CST change from baseline, µm	–25.5
CST change from baseline (min, max), µm	–117, +32
Total number of rescue injections,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

Anatomic Improvements and BCVA Maintained

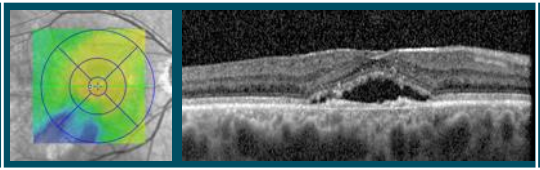
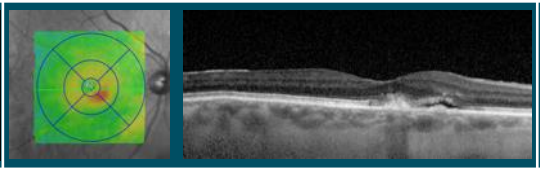
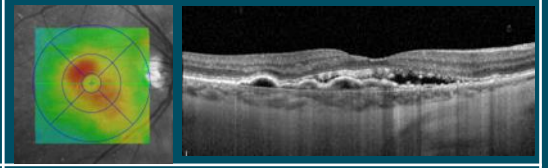
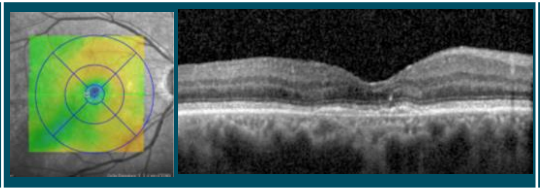
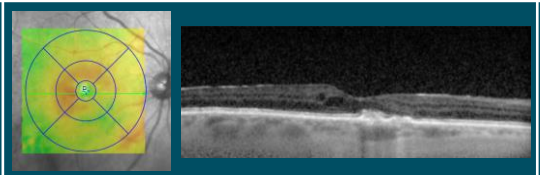
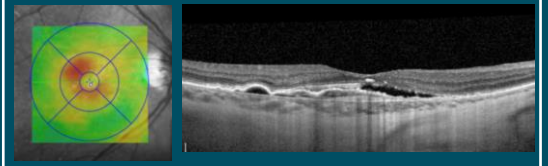
Additional Follow-up Through December 1, 2019

	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**

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

Anatomic Improvements and BCVA Maintained

Additional 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**

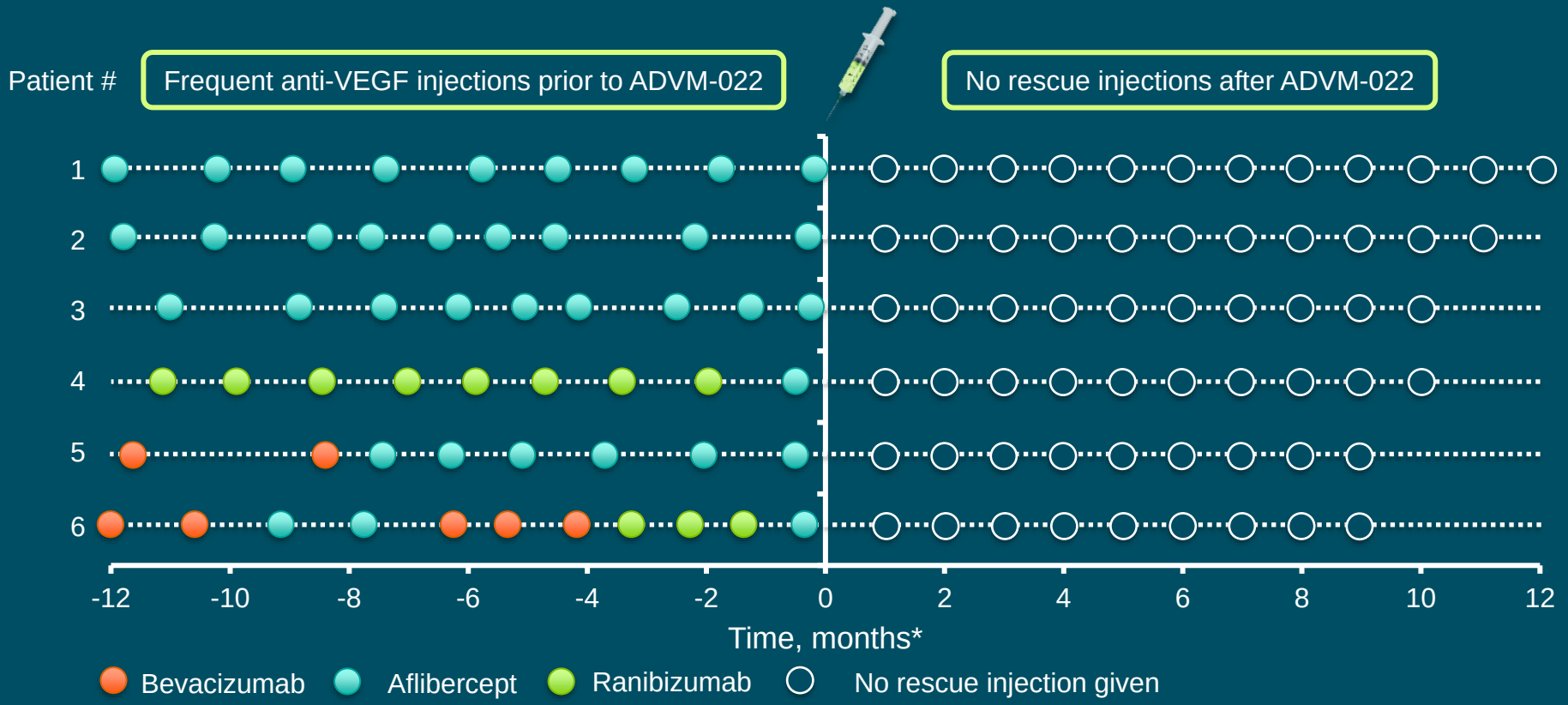
*BCVA, CST and OCT images for patient with retinal detachment (unrelated to study treatment) uses last observations prior to detachment (week 36)

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

IVT, intravitreal therapy; OCT, optical coherence tomography

No Anti-VEGF Injections Required After ADVM-022

Median 44 Weeks Follow-up



*Time relative to ADVM-022 injection date

OPTIC Cohort 1 Conclusions

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

- Mean BCVA and CST maintained
- Low-grade ocular inflammation responsive to steroid eyedrops
  - Cohorts 3 and 4 utilize 6-week prophylactic steroid eye drop regimen
- Zero rescue injections required
- ADVM-022 has the 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 Outlook

- OPTIC (nAMD)
  - Cohort 2 completed enrollment
  - Cohort 3 enrollment open
    - ADVM-022 ($2x10^{11}$vg/eye) with steroid eye drops prophylaxis
  - Cohort 4 enrollment Q1 2020
    - ADVM-022 ($6x10^{11}$vg/eye) with steroid eye drops prophylaxis
  - Cohort 1 52-week data H1 2020
  - Cohort 2 24-week data: Angiogenesis, Exudation and Degeneration February 8, 2020

- IND submission in diabetic retinopathy H1 2020 and study start H2 2020

H, half of year; IND, investigational new drug program; nAMD, neovascular age-related macular degeneration; Q, quarter of year

ADVM-022 Acknowledgments

Investigators, study teams and participants

- David Boyer MD
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