Phase 1 Study of Intravitreal Gene Therapy with ADVM-022 for Neovascular Age-related Macular Degeneration (OPTIC Trial Cohorts 1–3)

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– On behalf of the OPTIC investigators –

OPTIC
Gene Therapy in nAMD

May 4, 2020

Disclosures

OPTIC
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- Grant support: Adverum, Allergan, Chengdu Kanghong, Genentech, Gyroscope, Gemini Therapeutics, Kodiak, Novartis, Iveric Bio, Opthea, Oxurion, Recens Medical, Roche, Regenxbio
- Consultant: Adverum, Allergan, Bausch and Lomb, Chengdu Kanghong, Eyepoint Pharmaceuticals, Genentech, Gyroscope, Gemini Therapeutics, Kodiak, Novartis, Opthea, Oxurion, Recens Medical, Regenxbio
- Speaker: Allergan, Novartis

Key Takeaways

OPTIC Gene Therapy in nAMD

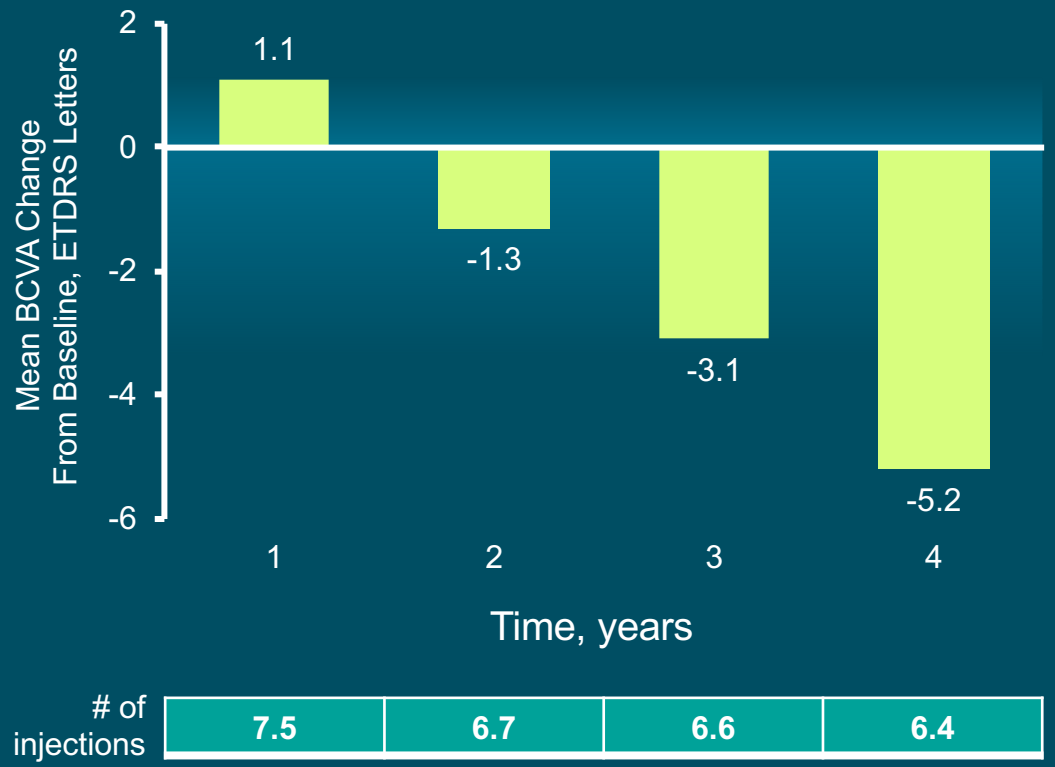
- ADVM-022 continues to be well tolerated and show robust efficacy
- Long-term durability beyond 1 year from a single IVT injection with zero rescue injections in Cohort 1
- Further evidence of a dose response at the $6x10^{11}$ vg/eye and $2x10^{11}$ vg/eye dose levels
- Evidence from Cohort 3 indicates that a 6-week prophylactic regimen of topical steroids is effective at minimizing early ocular inflammation
- Robust early response in Cohort 3, first 5 patients with 20 weeks follow up show:
  - BCVA improvement (+6.8 letters)
  - CST reduction (–137.8µm)

Data cut as of April 1, 2020
BCVA, best-corrected visual acuity; CST, central subfield thickness; IVT, intravitreal therapy

Real-world Anti-VEGF Patient Outcomes

Undertreatment Leads to Vision Loss

98,821 Eyes From 79,885 US Patients
Receiving Routine Intravitreal Anti-VEGF Therapy



Development Approach to Deliver
Long-term Efficacy

Gene therapy

In-office intravitreal injection to establish an intraocular anti-VEGF biofactory

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

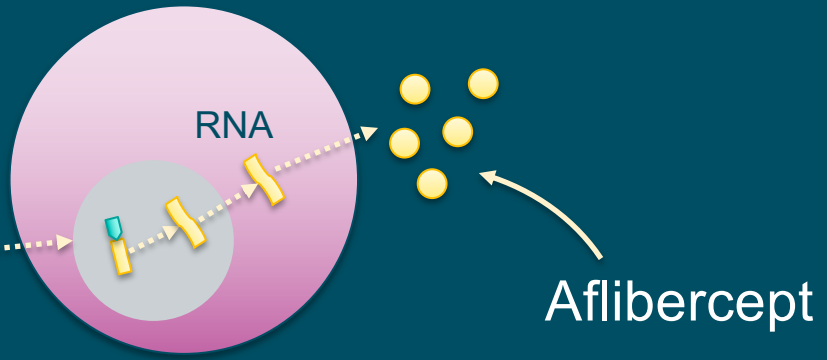
Khanani AM, et al. Ophthalmology Retina 2020;4:122-13

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

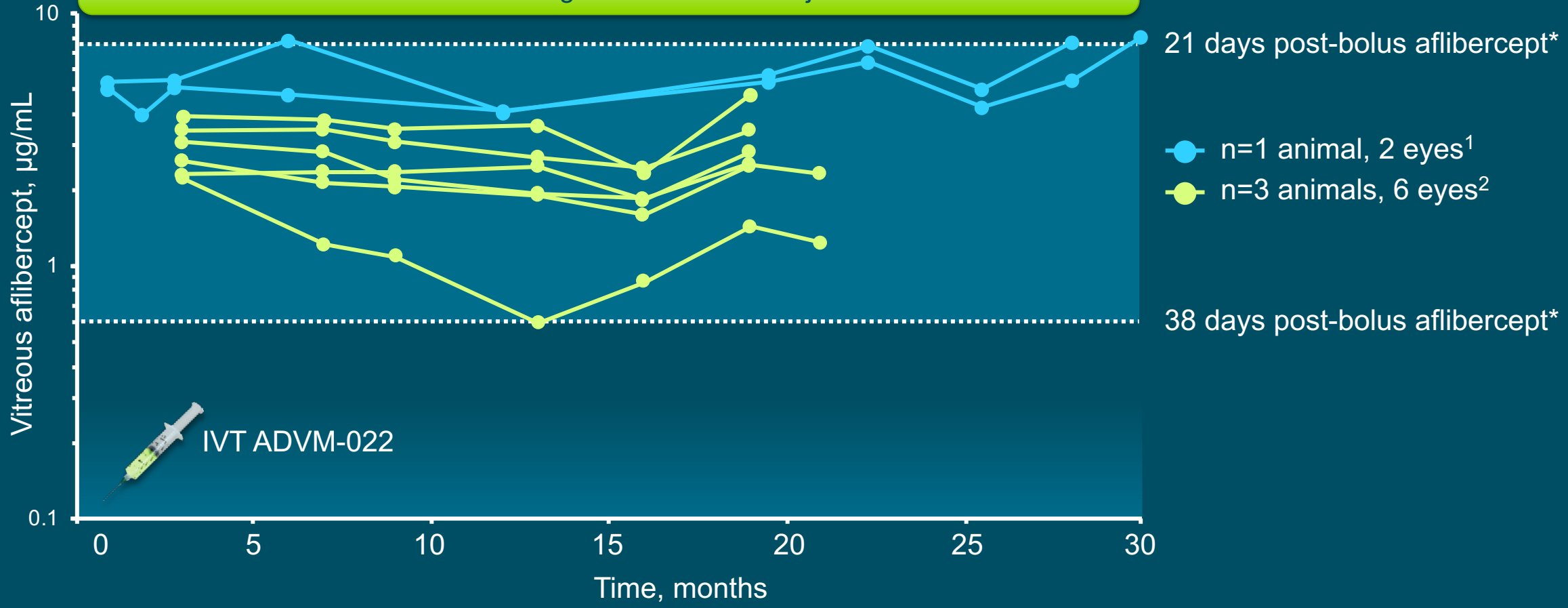
IVT, intravitreal

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

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

OPTIC Gene Therapy in nAMD

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

IVT, intravitreal therapy; 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

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

OPTIC Gene Therapy in nAMD

- 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

OPTIC Update for Cohorts 1–3 as of April 1, 2020

OPTIC
Gene Therapy in nAMD

	Cohort 1 (N=6)	Cohort 2 (N=6)	Cohort 3 (N=9)
ADVM-022 dose, vg/eye	6×10^{11}	2×10^{11}	2×10^{11}
Steroid prophylaxis	Oral 13-day course	Oral 13-day course	Eye drops 6-week course
Follow-up, weeks	52–64 (median 60)	32–40 (median 36)	4–20 (median 20)
Baseline characteristics	✓	✓	✓
Safety	✓	✓	✓
Efficacy†	✓	✓	First 5 patients*

*First 5 patients all had 20 weeks of follow-up as of April 1, 2020
Remaining 4 patients had 4–12 weeks of follow-up, insufficient for assessment of efficacy
†Includes BCVA and CST outcomes and need for rescue anti-VEGF

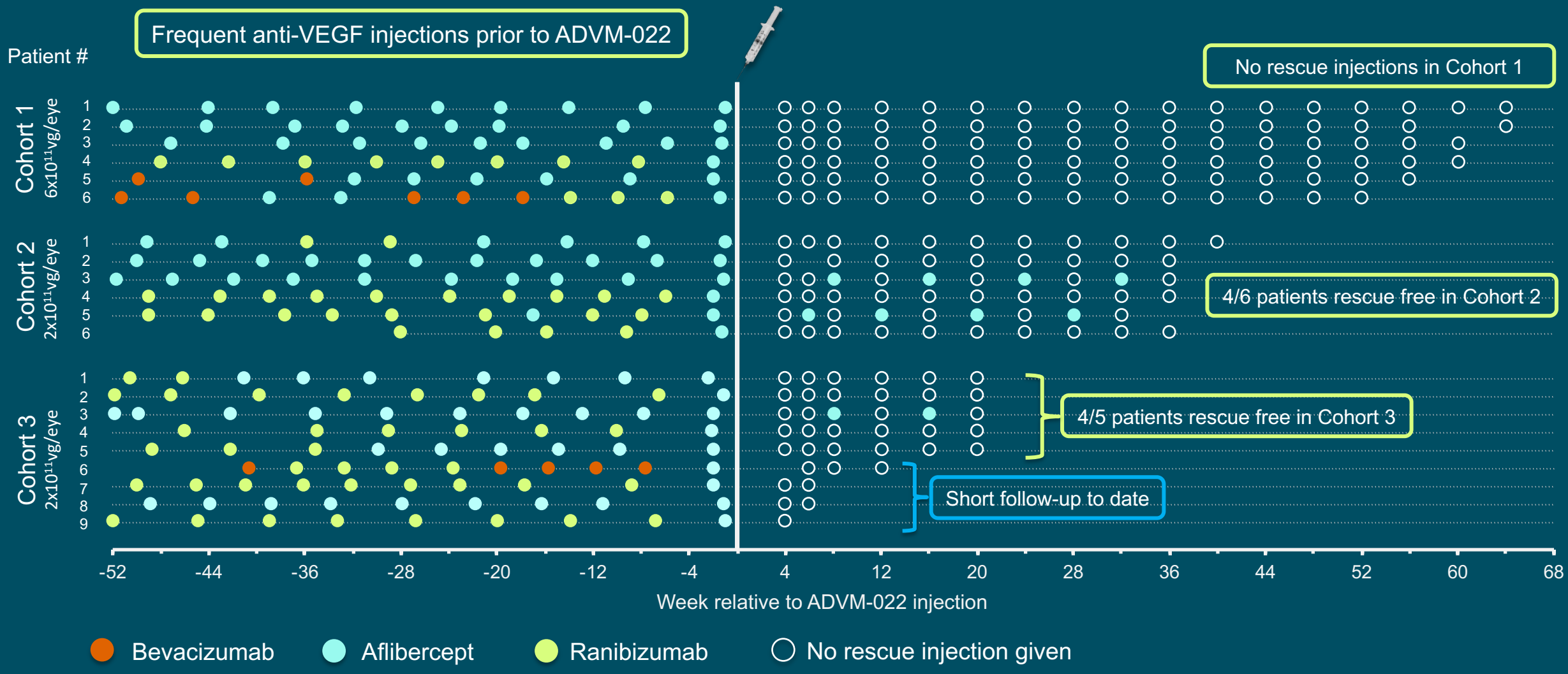
Study Population Previously Required Frequent Injections to Maintain Vision

Baseline Characteristics	Cohort 1 (N=6)	Cohort 2 (N=6)	Cohort 3 (N=9)
Mean age, years	79.0	79.8	77.4
Mean years since nAMD diagnosis	3.5	4.1	3.3
Mean (range) number anti-VEGF injections since initial diagnosis	35.3 (7–109)	34.0 (4–69)	24.8 (9–70)
Mean number anti-VEGF injections in 12 months prior to ADVM-022	9.2	9.2	9.1
Mean BCVA study eye, ETDRS letters Approximate Snellen equivalent	65.8 20/50	64.7 20/50	65.9 20/50
Mean CST study eye, µm	369.2	307.7	472.3

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

Long-term Durability with Zero Rescue Injections in Cohort 1
8/11* Patients Rescue-free across Cohorts 2 and 3

OPTIC
Gene Therapy in nAMD



*5/6 patients from Cohort 2 and 4/5 patients from Cohort 3 with 20 weeks follow-up

Data cut: April 1, 2020

Safety Summary Across Cohorts through April 1, 2020

- No ADVM-022 or procedure-related serious adverse events (SAEs)
- No ADVM-022-related non-ocular adverse events
- Low-grade inflammation commonly observed:
  - Responsive to topical steroids
  - No clinical or fluorescein* evidence of vasculitis, retinitis, or choroiditis
- Unrelated ocular SAE of retinal detachment surgically repaired and resolved
- Two patients had mild AEs of IOP elevation that resolved:
  - One patient had two mild IOP elevations (highest 24mmHg) that were both treated with Combigan® eye drops
  - One case in a patient on Combigan® for ocular hypertension at baseline which resolved with no change to treatment

*Fluorescein angiography of posterior pole
IOP, intraocular pressure; AEs, adverse events SAEs, serious AEs

Adverse Events Across Cohorts through April 1, 2020

Adverse events		Cohort 1 (N=6) 6×10^{11} vg/eye Oral steroids 13-day prophylaxis		Cohort 2 (N=6) 2×10^{11} vg/eye Oral steroids 13-day prophylaxis		Cohort 3 (N=9) 2×10^{11} vg/eye Steroid eye drops 6-week prophylaxis	
		Subjects	Events	Subjects	Events	Subjects	Events
Ocular	Serious	1	1*	0	0	0	0
	ADVM-022 related**	6	29	5	21	4	8
	Total ocular	6	49	5	32	7	16
Non-ocular†	Serious ‡	1	1	0	0	2	2
	Total non-ocular†	5	17	5	5	4	6

* Retinal detachment (unrelated to ADVM-022)

** ADVM-022 related ocular events were mild (69%) or moderate (31%)

† None of the non-ocular AEs were ADVM-022 related

‡ Serious non-ocular AEs included degenerative intervertebral disc disease (1) in Cohort 1; and COPD exacerbation (1), and stable angina pectoris (1) in Cohort 3

Cellular Inflammation Assessed by Slit Lamp Examination

Cohort 1: Low Grade and Responsive to Topical Steroids

OPTIC Gene Therapy in nAMD

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
QD: once daily; BID: twice daily; TID: three times daily; QID: four times daily

Data cut: April 1, 2020

Cellular Inflammation Assessed by Slit Lamp Examination

Cohort 2: Inflammation Responsive to and Managed with Topical Steroids

OPTIC Gene Therapy in nAMD

Aqueous cell grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria: Jabs DA, et al. J Ophthalmol 2005;140:509–516
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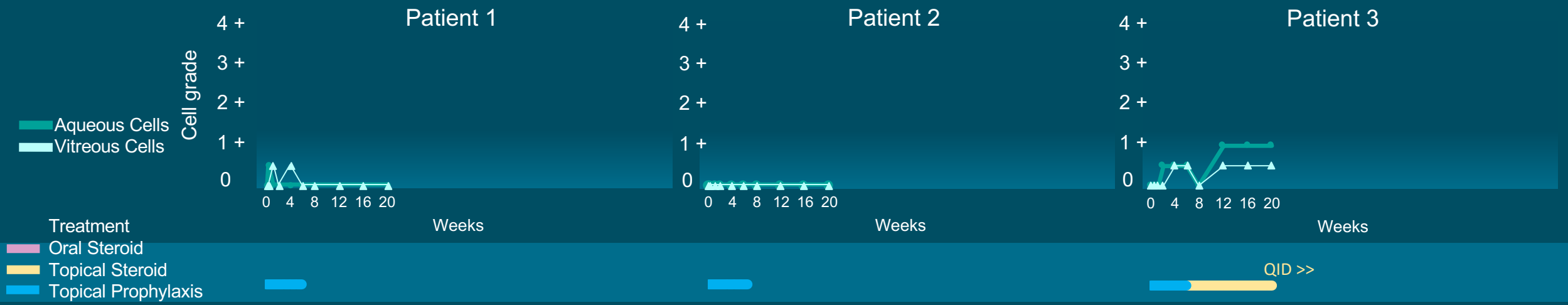
QD: once daily; BID: twice daily; TID: three times daily; QID: four times daily

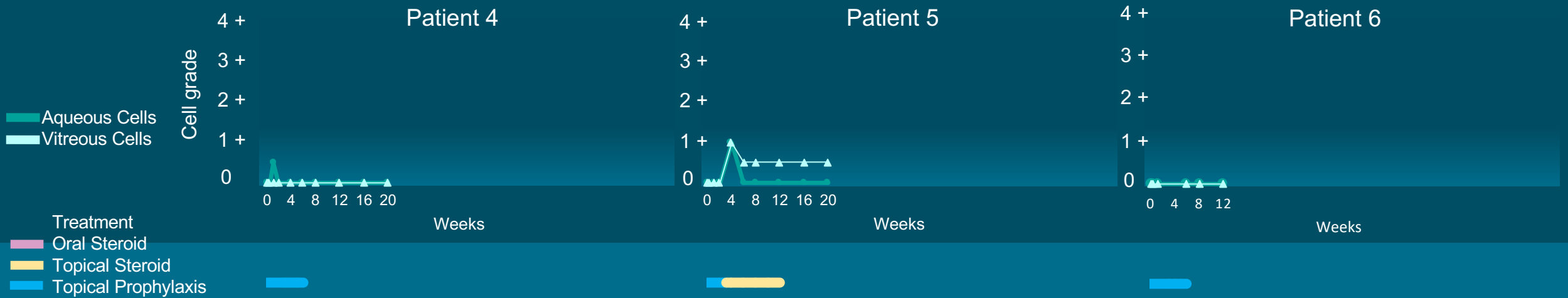
Data cut: April 1, 2020

Cellular Inflammation Assessed by Slit Lamp Examination

Cohort 3 (patients 1-6): Minimal Inflammation with Steroid Eye Drops Prophylaxis

OPTIC Gene Therapy in nAMD





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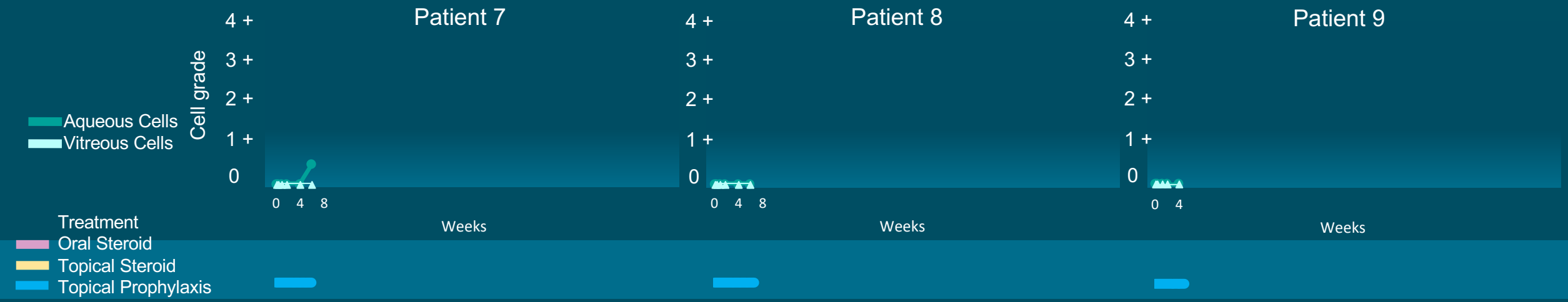
QD: once daily; BID: twice daily; TID: three times daily; QID: four times daily

Data cut: April 1, 2020

Cellular Inflammation Assessed by Slit Lamp Examination

Cohort 3 (patients 7-9): Minimal Inflammation with Steroid Eye Drops Prophylaxis



Patients 7-9 Notes:

- Short duration follow-up of 4-6 weeks following ADVM-022 administration
- Minimal early inflammation observed

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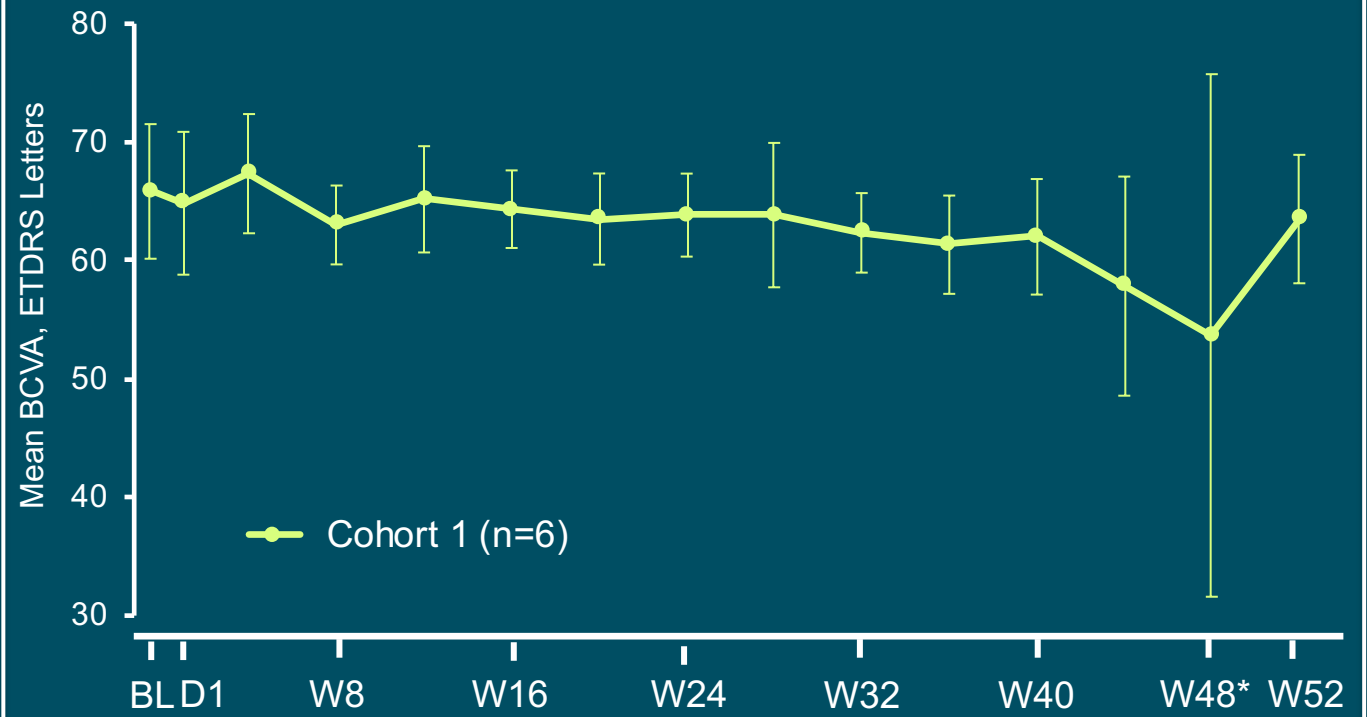
QD: once daily; BID: twice daily; TID: three times daily; QID: four times daily

Data cut: April 1, 2020

Cohort 1: BCVA Over Time

OPTIC
Gene Therapy in nAMD

Mean (90% CI) by Visit through Week 52



Latest Outcomes through April 1, 2020

Follow-up	52–64 weeks (median 60)
Rescue-free patients	100% (6/6)
Mean BCVA change from baseline:	
All patients:	–2.7 letters

Aflibercept 2mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1); *One patient had low BCVA scores at 44 and 48 weeks due to retinal detachment
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

Cohort 1: CST Over Time

Mean (90% CI) by Visit through Week 52

Latest Outcomes through April 1, 2020	
Follow-up	52–64 weeks (median 60)
Rescue-free patients	100% (6/6)
Mean CST change from baseline:	
All patients:	–26.2µm

Aflibercept 2mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1); *One patient had no CST data at 44 and 48 weeks due to retinal detachment
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

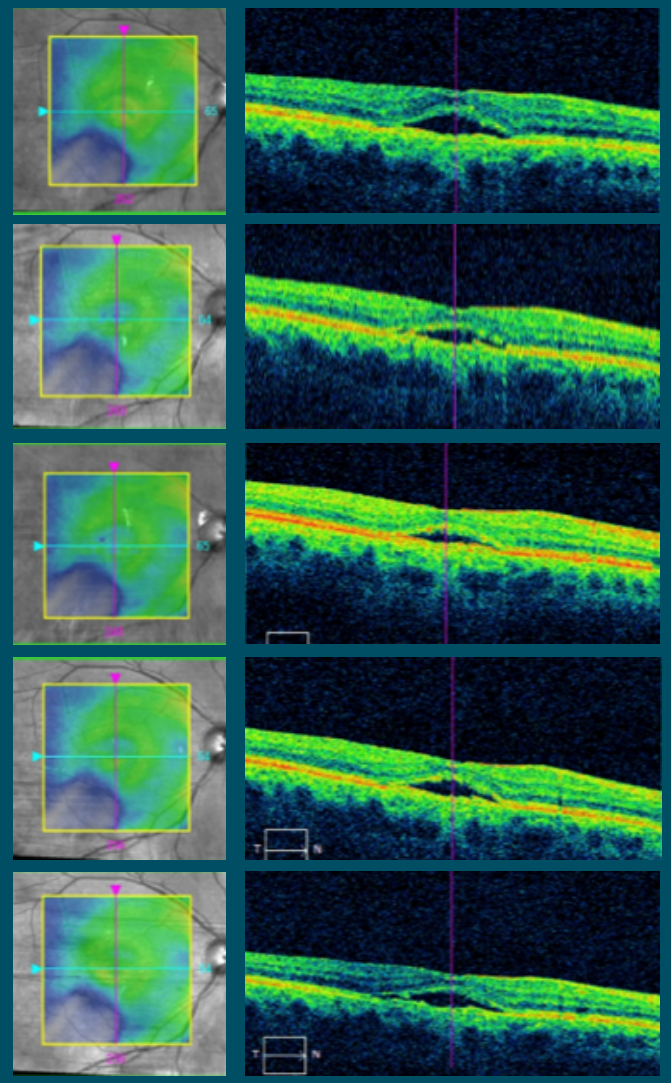
Case Study: Cohort 1, Subject 4

Anti-VEGF Centurion (>100 Injections)

OPTIC Gene Therapy in nAMD

OCT scans and treatment intervals from most recent 5 anti-VEGF injections visits prior to OPTIC

62 year old male	
Previous IVT, n	109
IVT in last 12 months, n	9



Weeks prior to ADVM-022

–30 weeks

–25 weeks

–20 weeks

–14 weeks

–8 weeks

Ranibizumab injections

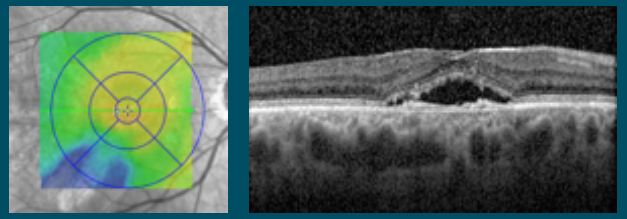
IVT, intravitreal therapy; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor

Case Study: Cohort 1, Subject 4

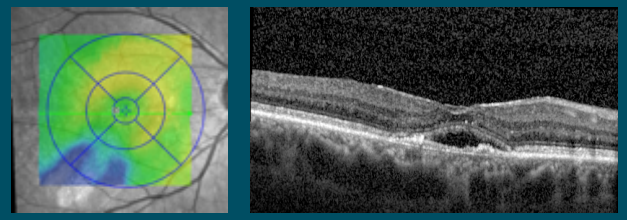
Durable response with no rescue injections through week 60

OPTIC Gene Therapy in nAMD

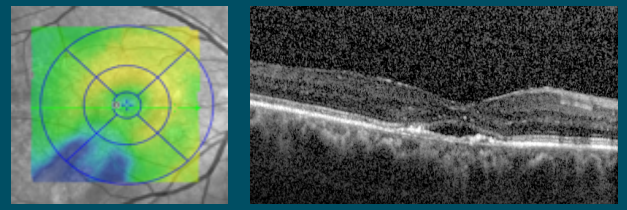
Aflibercept IVT
–2 weeks
BCVA: 65 letters
CST: 335 µm



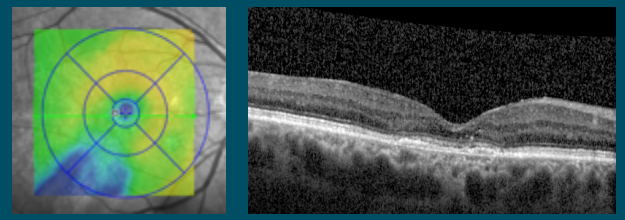
ADVM-022
Day 1
BCVA: 59 letters
CST: 268 µm



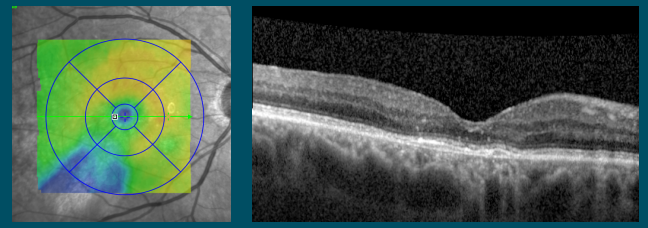
Week 4
BCVA: 75 letters
CST: 247µm



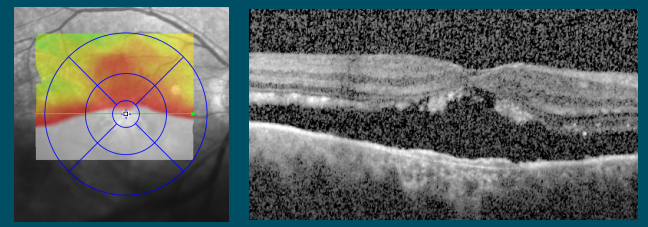
Week 12
BCVA: 70 letters
CST: 213µm



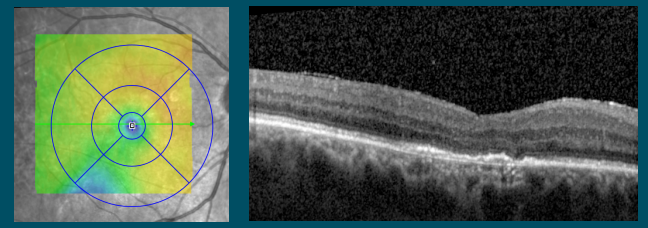
Week 32
BCVA: 70 letters
CST: 216µm



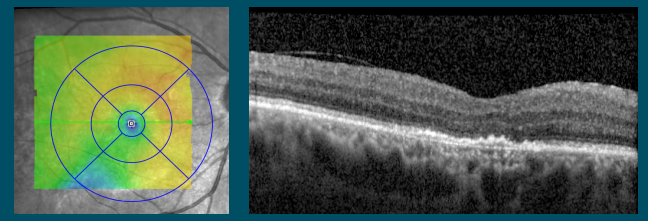
Week 44*
BCVA: 37 letters
CST (ungradable)



Week 52
BCVA: 59 letters
CST: 209µm



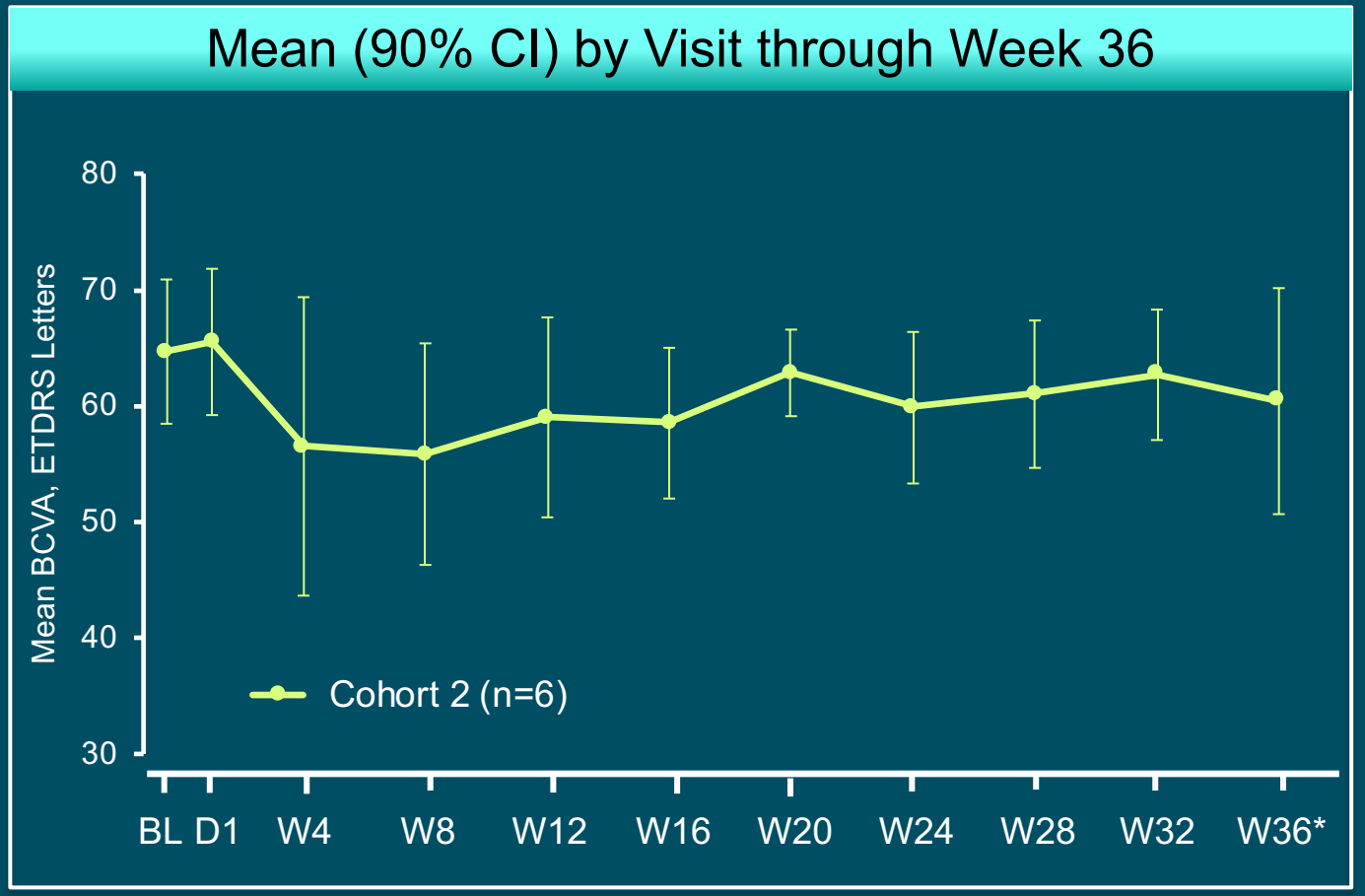
Week 60
BCVA: 55 letters
CST: 223µm



*Retinal detachment unrelated to ADVM-022
BCVA, best-corrected visual acuity; CST, central subfield thickness;
IVT, intravitreal injection

Cohort 2: BCVA Over Time

Mean (90% CI) by Visit through Week 36



Latest Outcomes through April 1, 2020

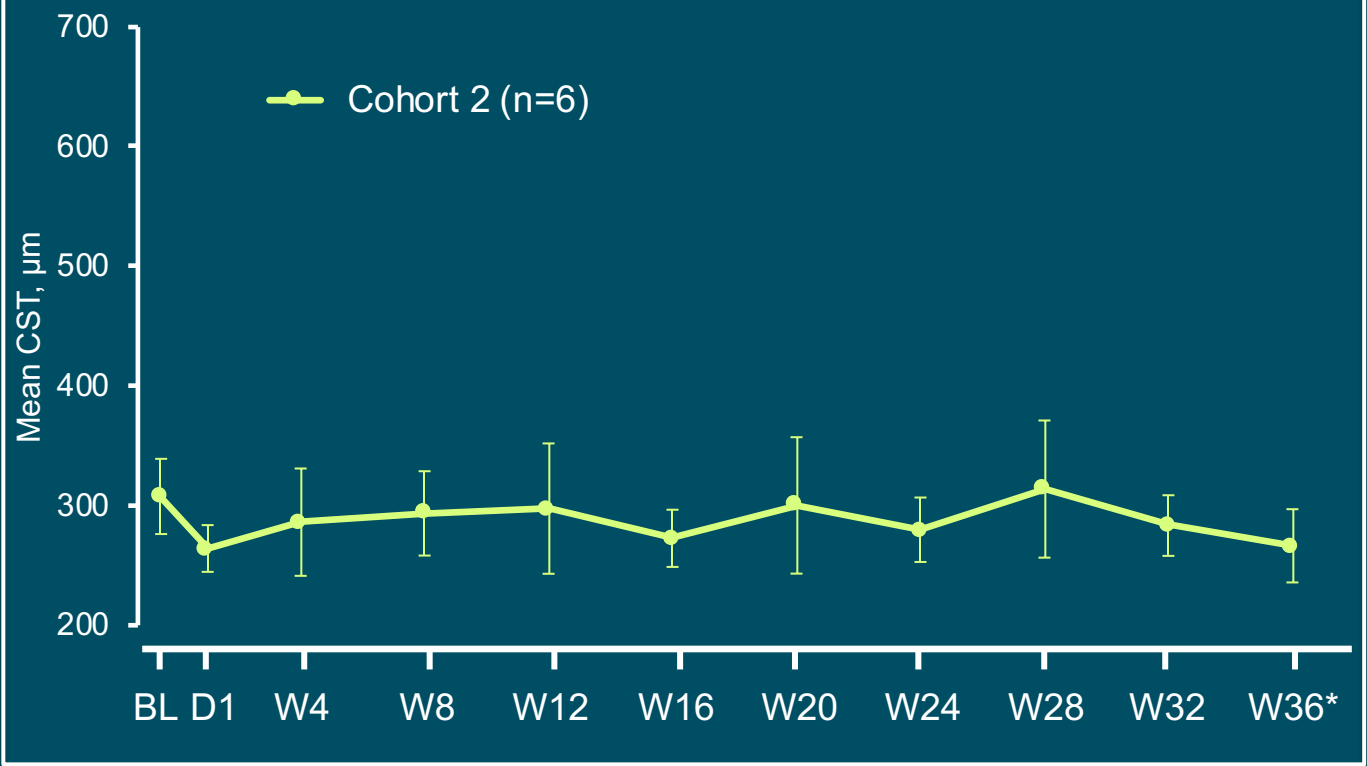
Follow-up	32–40 weeks (median 36)
Rescue-free patients	67% (4/6)
Mean BCVA change from baseline:	
All patients:	–2.8 letters
Rescue-free patients:	+2.3 letters

Aflibercept 2mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1); *One patient missed Week 36 visit.
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

Cohort 2: CST Over Time

OPTIC Gene Therapy in nAMD

Mean (90% CI) by Visit through Week 36



Latest Outcomes through April 1, 2020

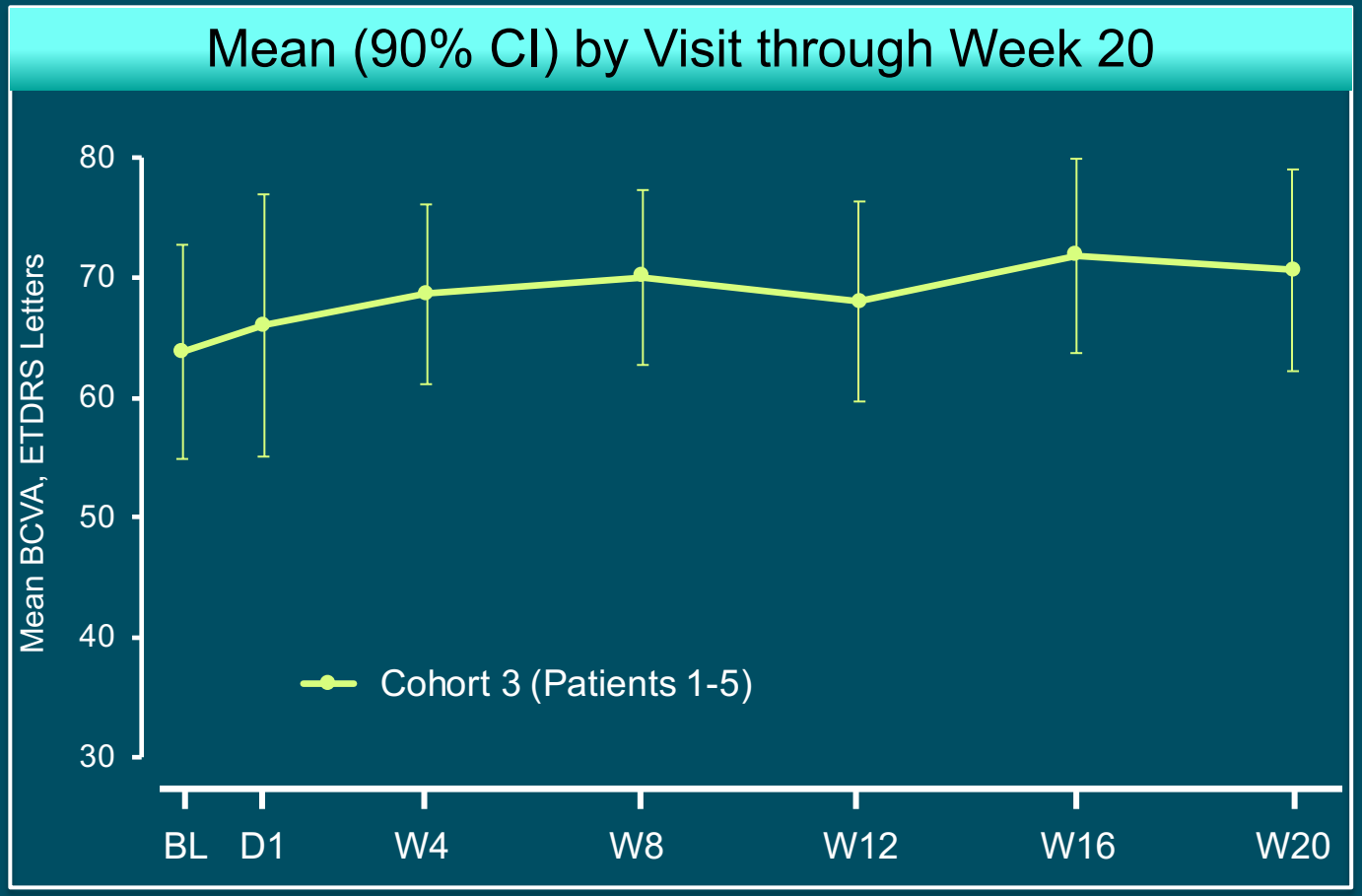
Follow-up	32–40 weeks (median 36)
Rescue-free patients	67% (4/6)
Mean CST change from baseline:	
All patients:	–40.8µm
Rescue-free patients:	–30.0µm

Aflibercept 2mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1); One patient missed Week 36 visit.
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

Cohort 3: BCVA Over Time (Patients 1-5)

OPTIC Gene Therapy in nAMD

Mean (90% CI) by Visit through Week 20



Latest Outcomes through April 1, 2020

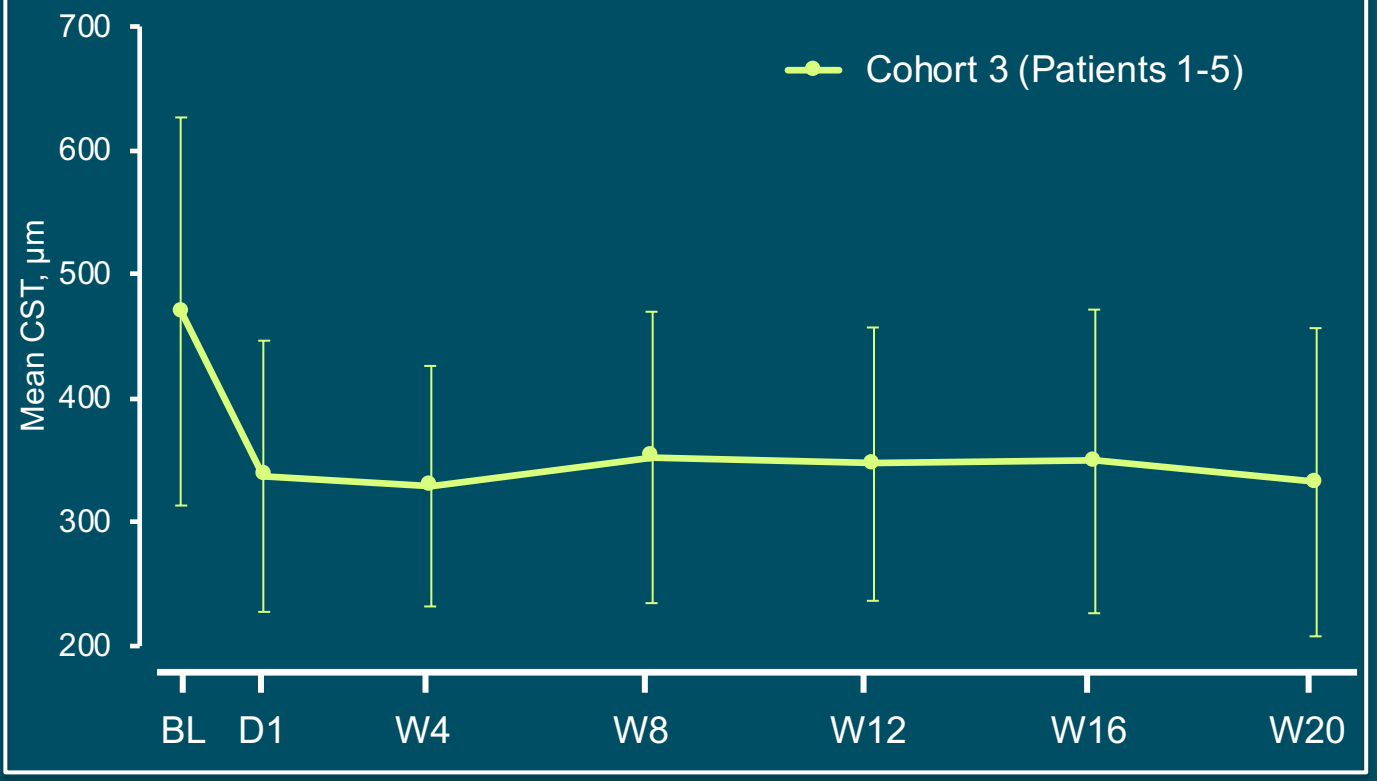
Follow-up	20 weeks for patients 1–5
Rescue-free patients	80% (4/5)
Mean BCVA change from baseline:	
All patients:	+6.8 letters
Rescue-free patients:	+8.8 letters

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

Cohort 3: CST Over Time (Patients 1-5)

OPTIC Gene Therapy in nAMD

Mean (90% CI) by Visit through Week 20



Latest Outcomes through April 1, 2020

Follow-up	20 weeks for patients 1–5
Rescue-free patients	80% (4/5)
Mean CST change from baseline:	
All patients:	–137.8µm
Rescue-free patients:	–149.8µm

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
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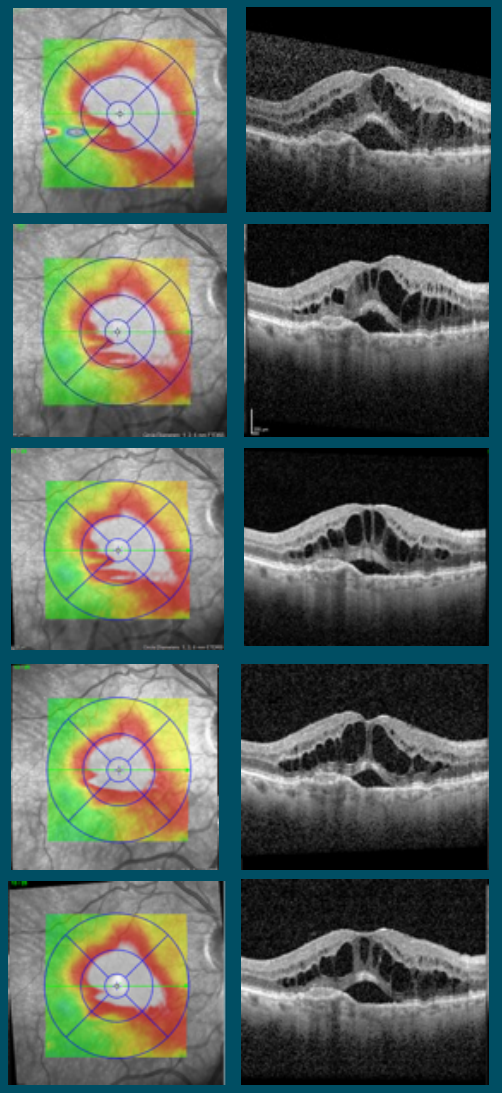
Case Study: Cohort 3, Subject 5

Persistent fluid despite frequent anti-VEGF injections

OPTIC Gene Therapy in nAMD

OCT scans and treatment intervals from most recent 5 anti-VEGF injections visits prior to OPTIC

82 year old male	
Previous IVT, n	19
IVT in last 12 months, n	9



Weeks prior to ADVM-022

–30 weeks

–25 weeks

–20 weeks

–15 weeks

–10 weeks

Aflibercept injections

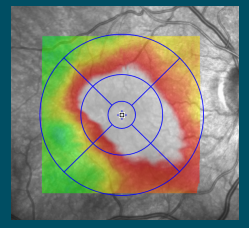
IVT, intravitreal therapy; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor

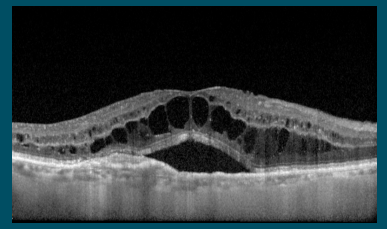
Case Study: Cohort 3, Subject 5

Rapid and sustained anatomical improvements

OPTIC Gene Therapy in nAMD

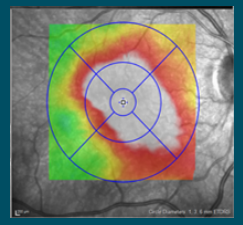
–3 weeks
Screening
BCVA: 77 letters
CST: 678µm

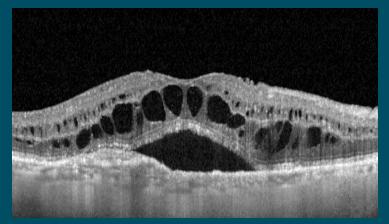




Aflibercept IVT

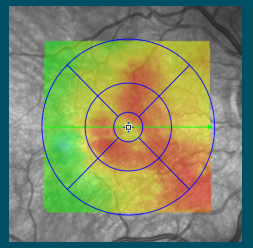
–2 weeks
BCVA: 75 letters
CST: 664 µm

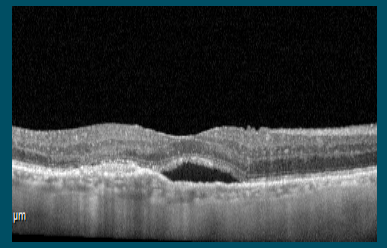




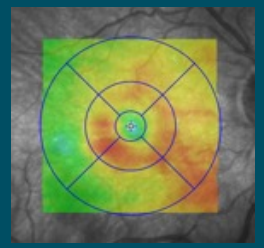
ADVM-022

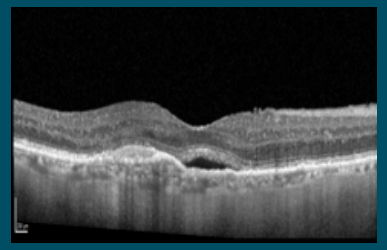
0 weeks
BCVA: 82 letters
CST: 355µm



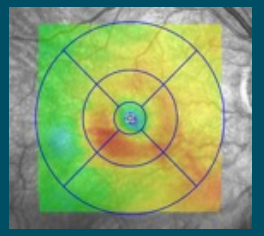


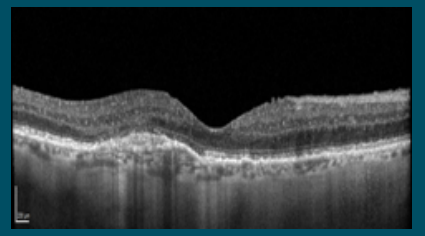
+1 week
BCVA: 80 letters
CST: 338µm



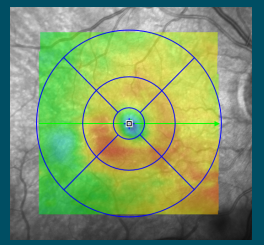


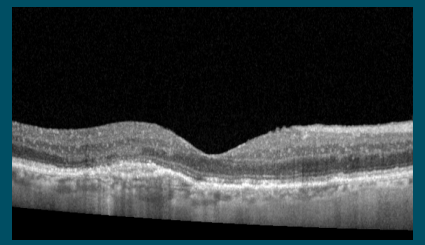
+6 weeks
BCVA: 79 letters
CST: 252µm



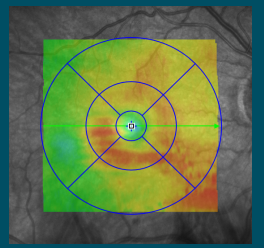


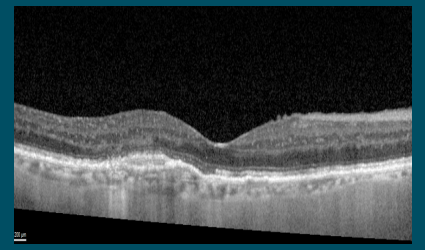
+12 weeks
BCVA: 81 letters
CST: 257µm



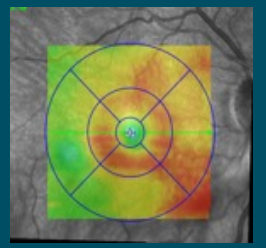


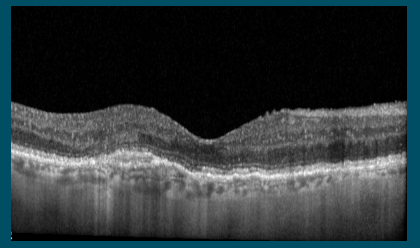
+16 weeks
BCVA: 82 letters
CST: 258µm





+20 weeks
BCVA: 82 letters
CST: 266µm

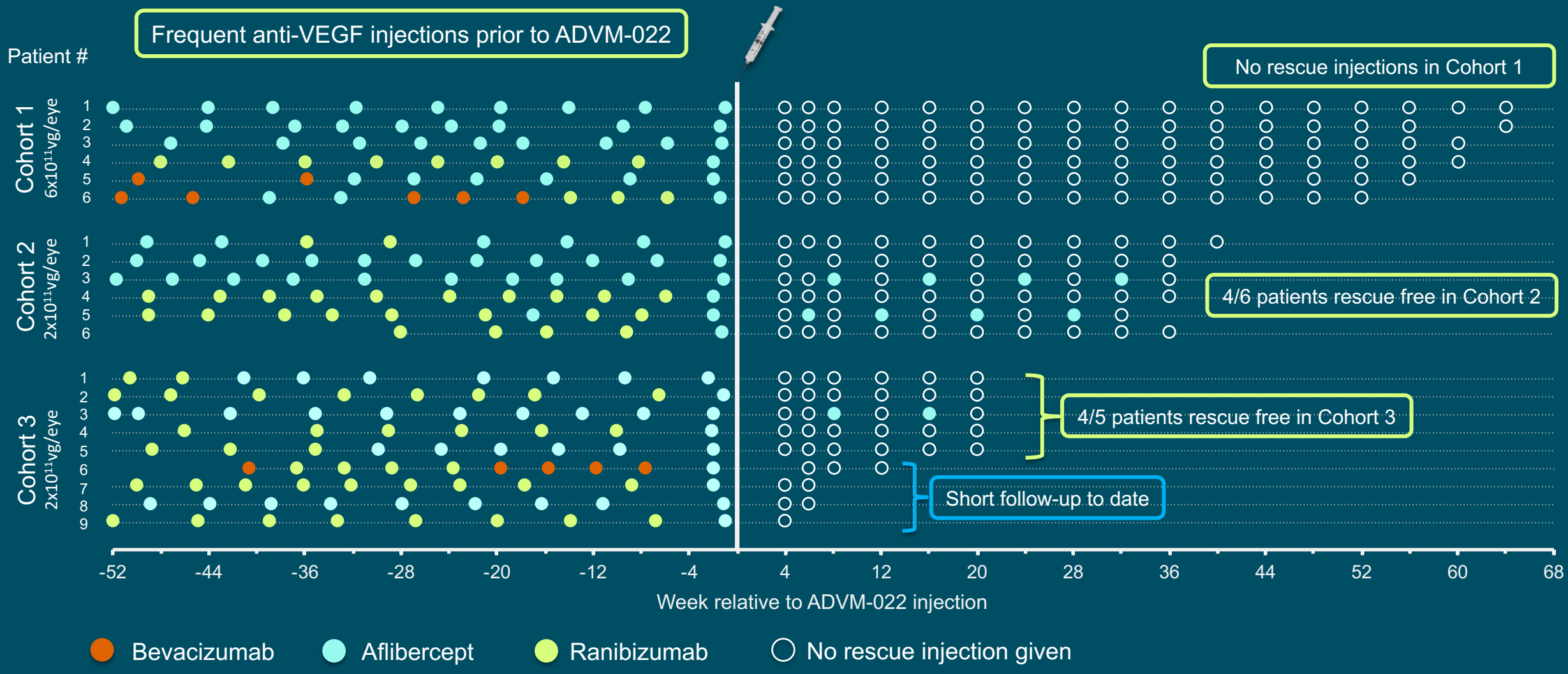




BCVA, best-corrected visual acuity; CST, central subfield thickness
IVT, intravitreal injection

Long-term Durability with Zero Rescue Injections in Cohort 1
8/11* Patients Rescue-free across Cohorts 2 and 3

OPTIC
Gene Therapy in nAMD



*5/6 patients from Cohort 2 and 4/5 patients from Cohort 3 with 20 weeks follow-up

Data cut: April 1, 2020

Conclusions

- ADVM-022 continues to be well tolerated and shows robust efficacy
- Long-term durability beyond 1 year from a single IVT injection with zero rescue injections in Cohort 1
- Further evidence of a dose response:
  - $6x10^{11}$vg/eye: 6/6 patients rescue injection free
  - $2x10^{11}$vg/eye: 8/11* patients rescue injection free
- Evidence from Cohort 3 indicates that a 6-week prophylactic regimen of steroid eye drops effective at minimizing early ocular inflammation
- Robust early response in Cohort 3, first 5 patients with 20 weeks follow up show:
  - BCVA improvement (+6.8 letters)
  - CST reduction (–137.8µm)
- ADVM-022 demonstrates further potential to greatly reduce anti-VEGF injection burden in neovascular AMD

*5/6 patients from Cohort 2 and 4/5 patients from Cohort 3 with 20 weeks follow-up
BCVA, best-corrected visual acuity; CST, central subfield thickness; IVT, intravitreal injection

Data cut as of April 1, 2020

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