Intravitreal Gene Therapy for Exudative AMD and Diabetic Retinopathy

Arshad M Khanani, M.D., M.A.

Director of Clinical Research, Sierra Eye Associates

(on behalf of the OPTIC investigators)

Angiogenesis, Exudation, and Degeneration 2021 • Virtual • February 12-13, 2021

Disclosures

- **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 for ADVM-022 (OPTIC Trial)

- Continues to be well tolerated with a favorable safety profile at both high and low doses
- Show robust and sustained efficacy at both high and low doses
- Durability out to 92 weeks from a single IVT injection with zero supplemental injections in Cohort 1
- Robust aqueous anti-VEGF protein expression observed at 18 months in Cohort 1
- Substantial reduction in annualized injection frequency following ADVM-022
- Most patients are supplemental injection free in OPTIC
- Warrant further investigation in larger studies

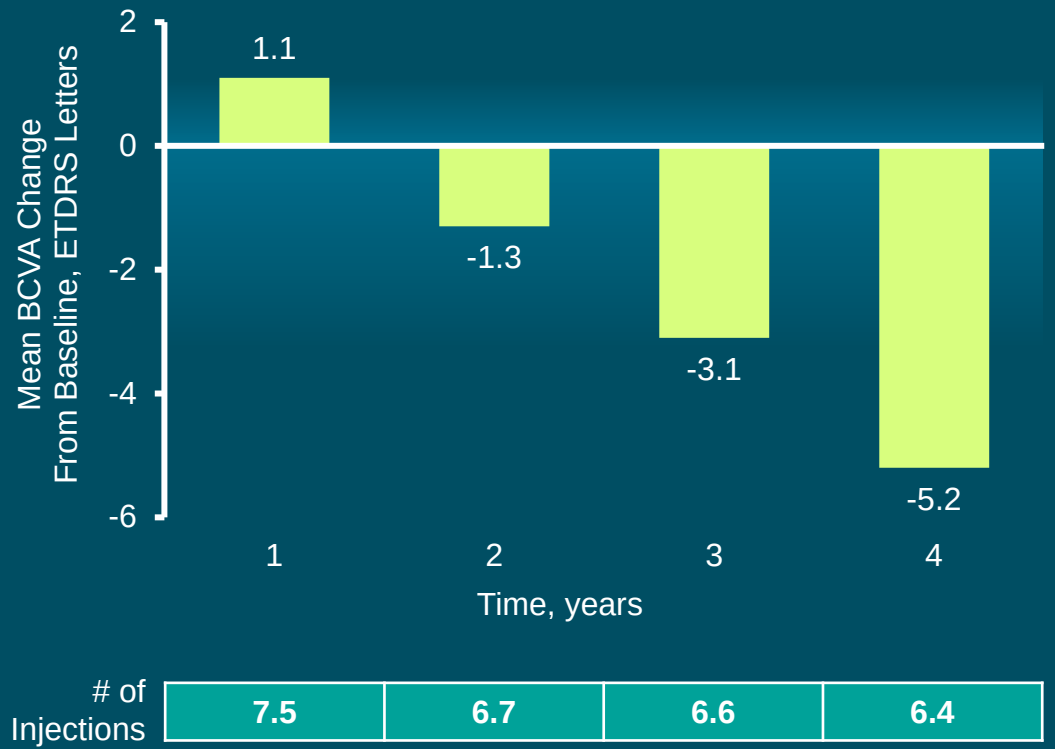
VEGF, vascular endothelial growth factor; IVT, intravitreal

Data cut: October 15, 2020

Real-world anti-VEGF Patient Outcomes

Under treatment leads to vision loss over time

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
VEGF, vascular endothelial growth factor

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

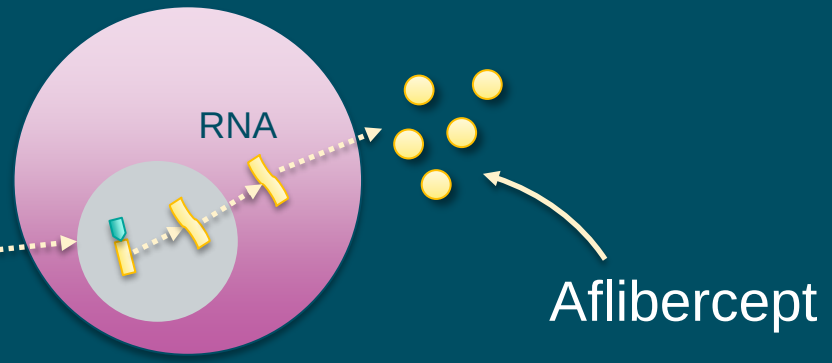
ADVM-022: Adeno-Associated Virus Gene Therapy Vector

Designed for continuous delivery of aflibercept 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

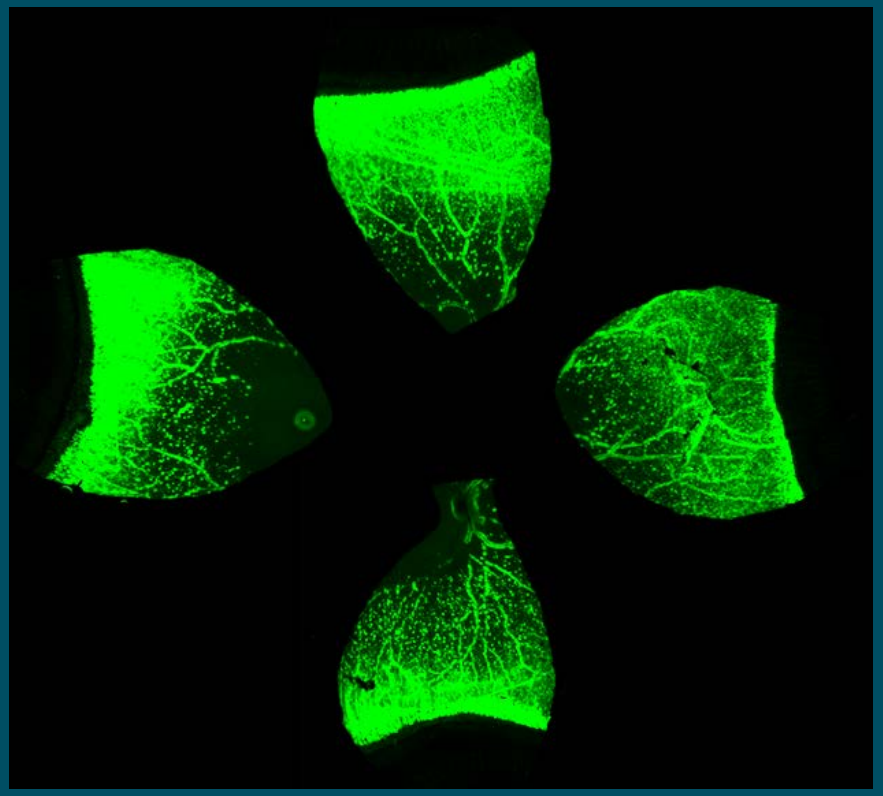
Codon-Optimized cDNA

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 (1.2 mg/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

- **Primary Objective**
  - Assess the safety and tolerability of a single IVT injection of ADVM-022
- **Secondary Objective**
  - 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 (2 mg 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 >75 µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

**Subjects received prophylaxis of 60 mg 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 1-4 as of October 15, 2020

	Cohort 1 (N=6)	Cohort 2 (N=6)	Cohort 3 (N=9)	Cohort 4* (N=9)
ADVM-022 Dose, vg/eye	**High Dose** 6×10^{11}	**Low Dose** 2×10^{11}	**Low Dose** 2×10^{11}	**High Dose** 6×10^{11}
Steroid Prophylaxis	**Oral** 13-day course	**Oral** 13-day course	**Eye drops** 6-week course	**Eye drops** 6-week course
Follow-Up, Weeks	64–92 weeks (median 86)	64–68 weeks (median 64)	32–48 weeks (median 48)	12–24 weeks (median 16)
Subject Disposition	No discontinuations, some visits missed due to COVID-19 concerns	No discontinuations	No discontinuations, some visits missed due to COVID-19 concerns	No discontinuations
Baseline Characteristics	✓	✓	✓	✓
Safety Data	✓	✓	✓	✓
Efficacy Data†	✓	✓	✓	N/A
Aqueous anti-VEGF Protein Expression Data	N=2 at week 76	N/A	N/A	N/A

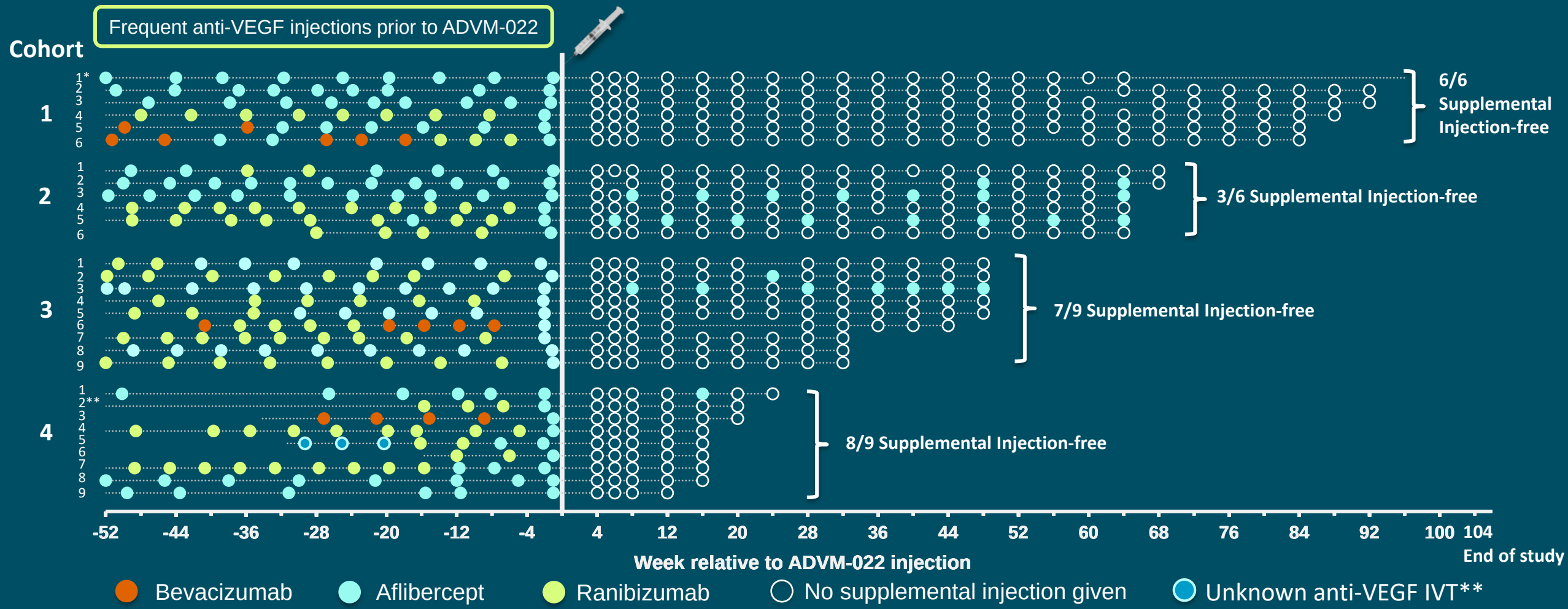
**Cohort 4 has less than 6 months of follow-up*
†Includes BCVA and CST outcomes

Neovascular AMD Study Population Previously Required Frequent Injections to Maintain Vision

Baseline Characteristics	Cohort 1 (N=6)	Cohort 2 (N=6)	Cohort 3 (N=9)	Cohort 4 (N=9)
Mean (range) Age, Years	79.0 (62–88)	79.8 (74–90)	77.4 (65–90)	79.9 (68–88)
Mean (range) Years Since nAMD Diagnosis	4.5 (0.9–10.6)	4.1 (0.5–6.8)	3.3 (0.7–8.0)	3.2 (0.2–8.0)
Mean (range) Number anti-VEGF Injections Since Initial Diagnosis*	38.2 (7–109)	34.0 (4–69)	24.8 (9–70)	28.5 (2–58)**
Mean (range) Number anti-VEGF Injections in 12 Months Prior to ADVM-022	9.2 (8–11)	9.2 (5–11)	9.1 (7–10)	7.1 (3–12)**
Mean (range) BCVA, ETDRS Letters Approximate Snellen Equivalent	65.8 (57–77) 20/50	64.7 (53–72) 20/50	65.9 (53–75) 20/50	65.0 (54–77) 20/50
Mean (range) CST, µm	369.2 (293–561)	307.7 (235–339)	473.4 (301–857)	398.6 (255–538)

**Not including the mandated aflibercept at Screening; **Excluding Patient #2 with incomplete prior anti-VEGF data.*
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

Substantial Reduction in anti-VEGF Treatments Following a Single IVT Injection of ADVM-022

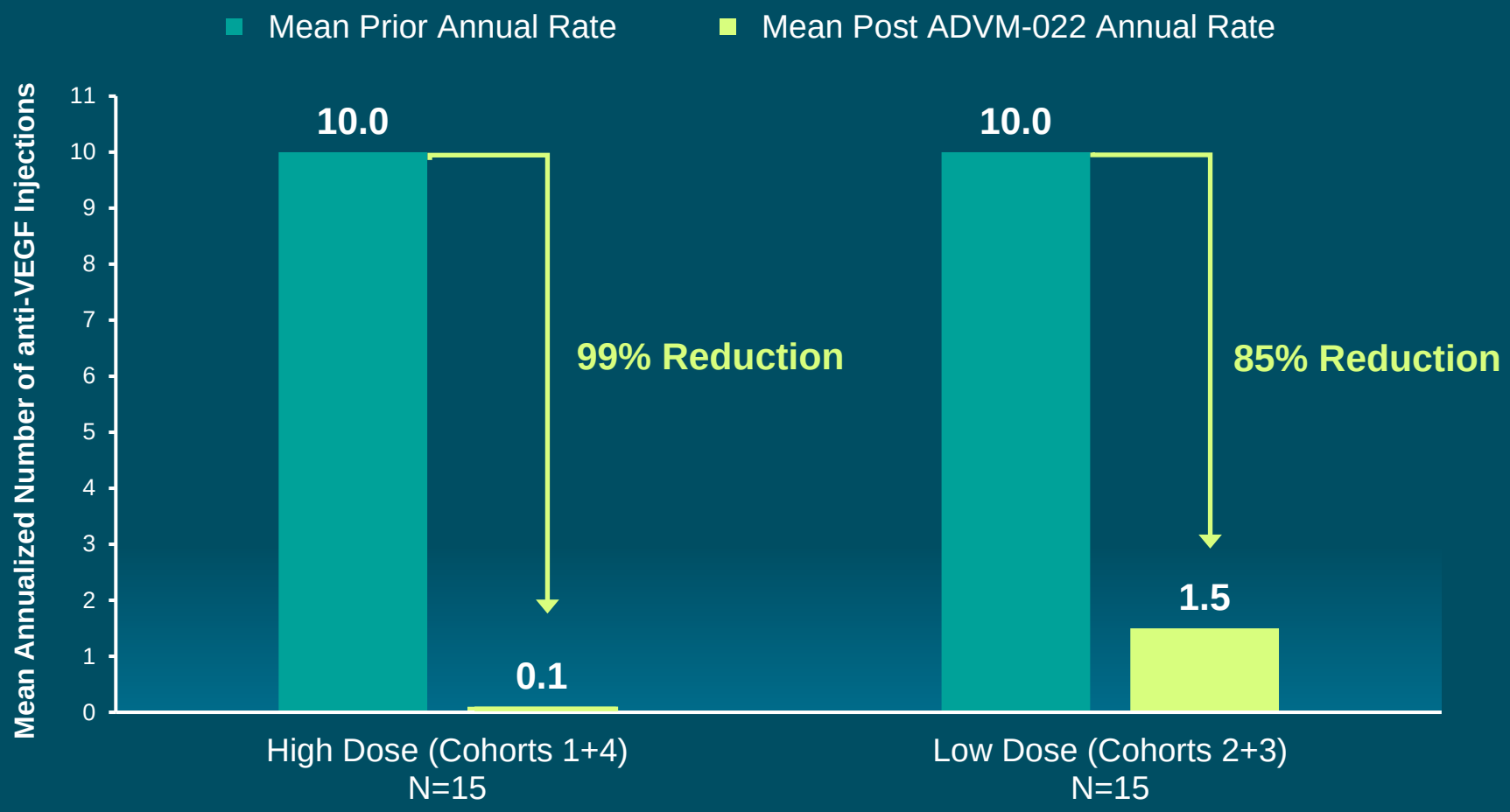


Five patients were diagnosed <1 year prior to ADVM-022 injection: one each in Cohorts 2 and 3, three in Cohort 4.

**Cohort 1, Patient 1 remains on study but have missed visits post Week 64; **Incomplete prior data for Cohort 4, Patient 2; †Received in a clinical trial not yet unmasked (NCT04049266).*

Data cut: October 15, 2020

Substantial Reduction in Annualized anti-VEGF Injection Frequency Following ADVM-022



Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).

Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).

Data cut: October 15, 2020

Safety Summary Across Cohorts through October 15, 2020

- No ADVM-022-related non-ocular adverse events
  - No deaths or discontinuations in OPTIC
- When observed, inflammation has been responsive to and manageable with steroid eye drops
- No clinical or fluorescein* evidence of posterior inflammation
  - No vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- All ADVM-022-related ocular AEs were mild (78%) to moderate (22%)
  - One AE of special interest of moderate recurrent uveitis deemed to be related to ADVM-022 was responsive to steroid eye drops (Cohort 1)
- One unrelated ocular SAE of retinal detachment surgically repaired and resolved (Cohort 1)
- Two patients had mild AEs of IOP elevation that resolved
  - One patient had two mild IOP elevations (highest 24 mmHg) 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 as of October 15, 2020

ADVM-022 related events were mild (78%) or moderate (22%)

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		Cohort 4 (N=9) 6×10^{11} vg/eye Steroid eye drops 6-week prophylaxis	
		Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ocular	Serious	2	2*	0	0	0	0	0	0
	ADVM-022 Related**	6	31	5	21	5	15	6	19
	Total Ocular	6	54	5	34	8	31	8	23
Non-Ocular†	Serious ‡	1	1	0	0	2	2	0	0
	Total Non-Ocular†	5	18	6	7	5	10	2	2

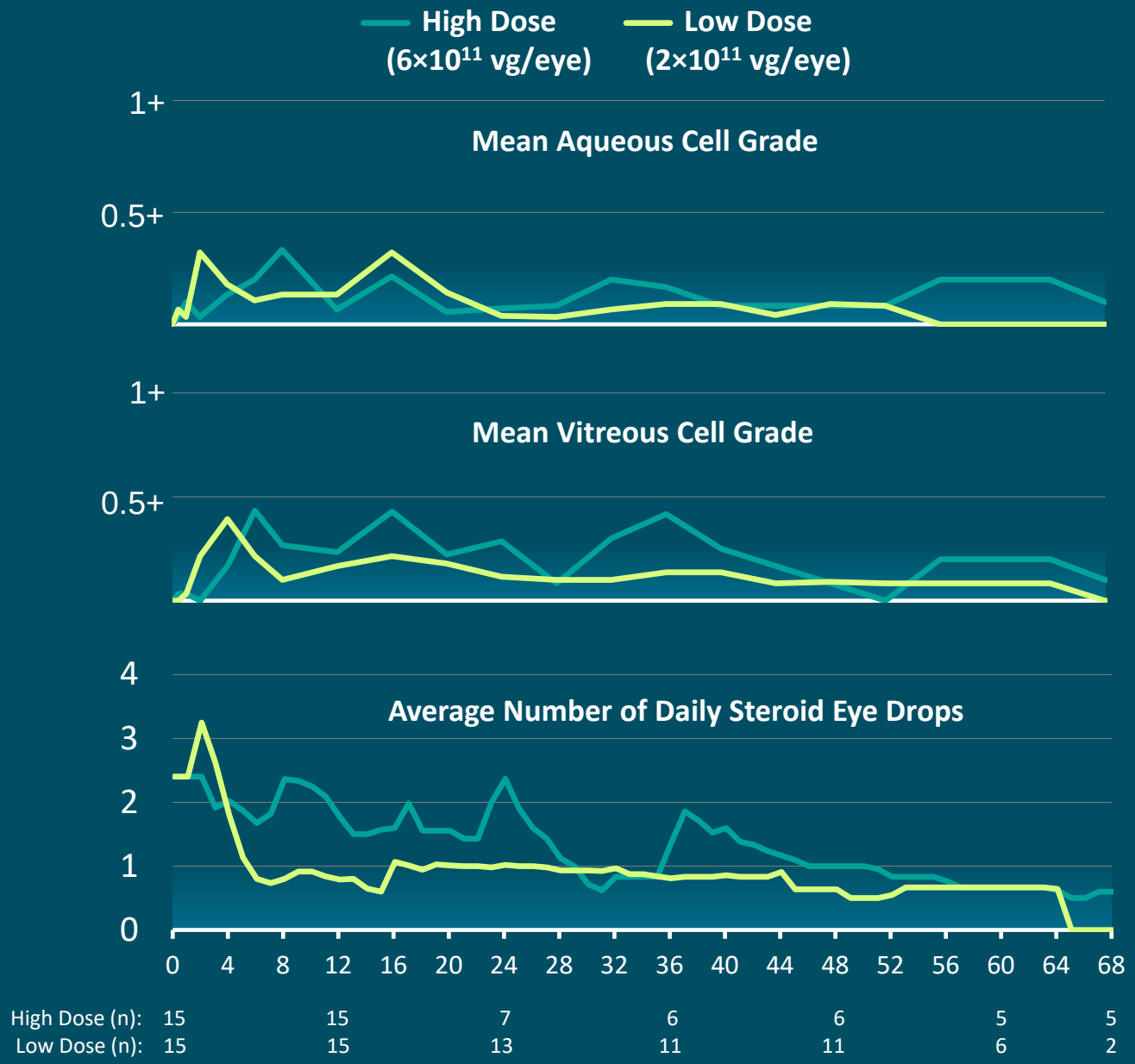
* *Retinal detachment (unrelated to ADVM-022) and recurrent moderate uveitis (likely related to ADVM-022)*

** *ADVM-022 related ocular events were mild (78%) or moderate (22%)*

† *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*

Ocular Cell Grade and Steroid Eye Drop Use Decreases over Time



Decreasing trend over time for:

- Average aqueous cell grade
- Average vitreous cell grade
- Average steroid eye drop use

Cell grades as assessed by slit lamp
Grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria for aqueous cells and National Institutes of Health (NIH) guidelines for vitreous cells.
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

Data through October 15, 2020

Ocular Cellular Inflammation & Topical Steroid Eye Drop Overview

Latest Outcomes as of October 15, 2020

Dose	Cohort 1 High Dose (N=6)	Cohort 2 Low Dose (N=6)	Cohort 3 Low Dose (N=9)	Cohort 4 High Dose (N=9)
Follow-Up	64–92 weeks (median 86)	64–68 weeks (median 64)	32–48 weeks (median 48)	12–24 weeks (median 16)
Average Aqueous Cell Grade	0.08	0.00	0.06	0.11
Average Vitreous Cell Grade	0.17	0.00	0.06	0.11
% with any cellular inflammation	33%	0%	11%	22%
Average # of daily drops	1.2	0.5	0.8	1.9

At the most recent visit:

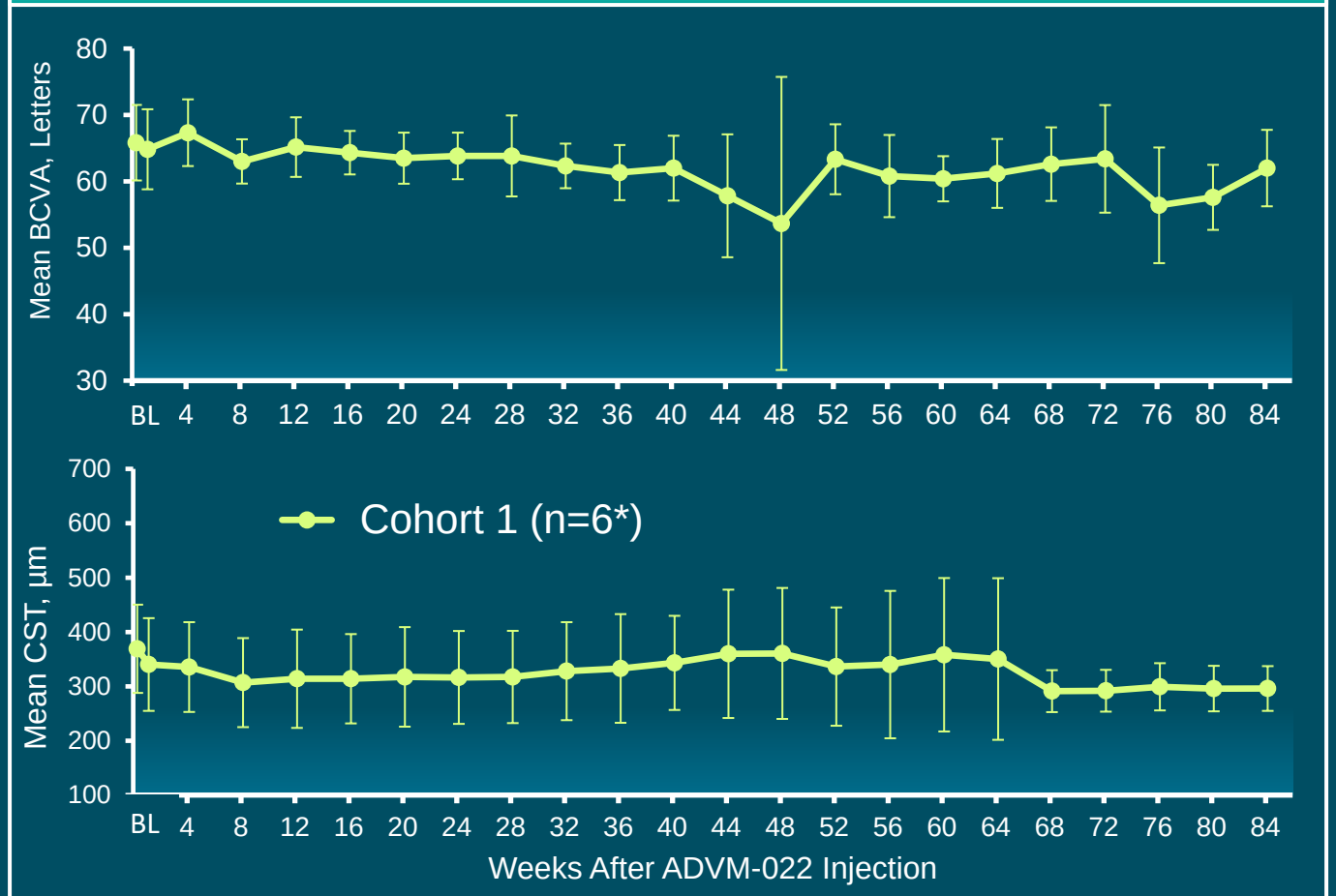
- Low average cell grades
- Low average number of daily drops
- Cohort 4 still in early follow-up
- Slow tapering implemented

High Dose - 6×10^{11} vg/eye
Low Dose - 2×10^{11} vg/eye
Averages calculated across entire cohort

Cohort 1: BCVA and CST Stable, Zero Supplemental Injections

Robust anti-VEGF Protein Expression observed at 18 months

Mean (90% CI) by Visit Through Week 84



Latest Outcomes as of Oct. 15, 2020

Follow-Up	64–92 weeks (median 86)
Rescue-Free Patients	100% (6/6)
Mean BCVA Change from Baseline	
All Patients	–2.5 Letters
Mean CST Change from Baseline	
All Patients	–19.7 µm

Mean Aqueous anti-VEGF Protein level**

Week 76 (n=2)	1840 ng/mL

**One patient had low BCVA and no CST values at 44 and 48 weeks due to retinal detachment; N=5 from Week 56 to 84*

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

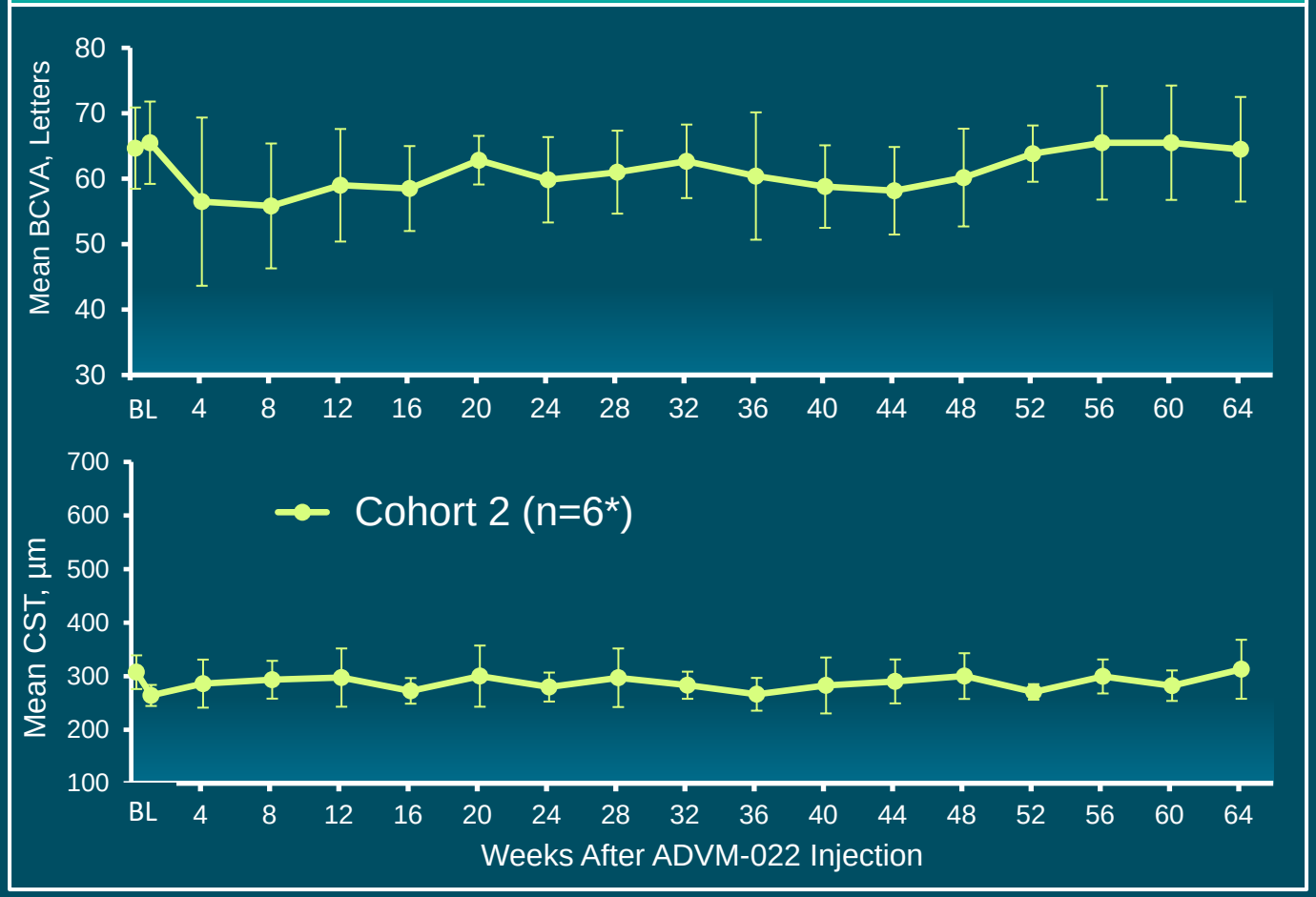
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week

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

*** Available aqueous humor aflibercept protein samples from Cohort 1 subjects enrolled in optional aqueous humor sampling study*

Cohort 2: BCVA and CST Maintained Over Time

Mean (90% CI) by Visit Through Week 64



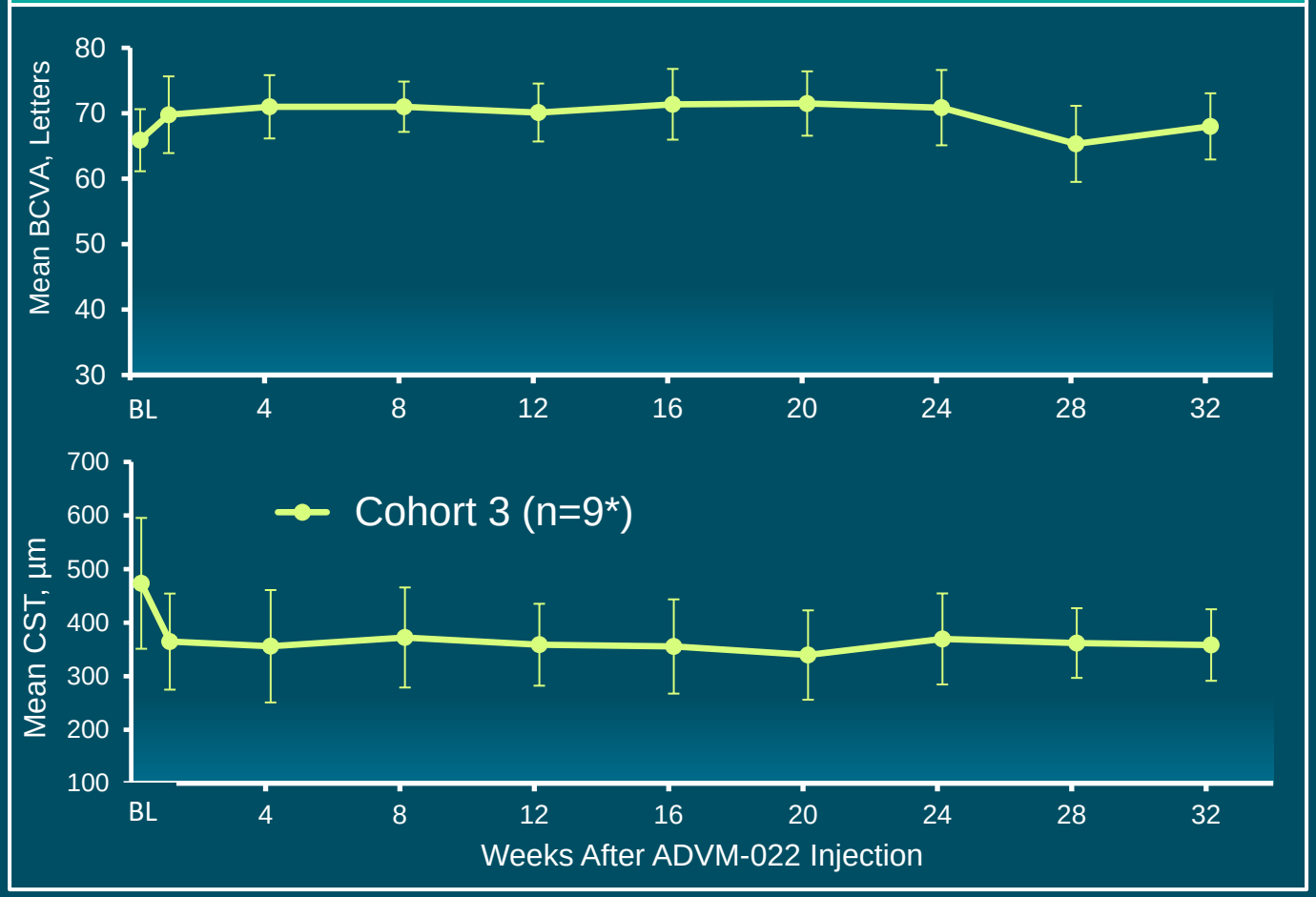
Latest Outcomes as of Oct. 15, 2020

Follow-Up	64–68 weeks (median 64)
Rescue-Free Patients	50% (3/6)
Mean BCVA Change from Baseline	
All Patients	+0.2 Letters
Rescue-Free Patients	+1.0 Letters
Mean CST Change from Baseline	
All Patients	–1.0 µm
Rescue-Free Patients	–23.7 µm

** N=5 for Week 36 and 40 visits*
Aflibercept 2 mg 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: BCVA Maintained and CST Improved

Mean (90% CI) by Visit Through Week 32



Latest Outcomes as of Oct. 15, 2020	
Follow-Up	32–48 weeks (median 48)
Rescue-Free Patients	78% (7/9)
Mean BCVA Change from Baseline	
All Patients	–0.9 Letters
Rescue-Free Patients	+4.1 Letters
Mean CST Change from Baseline	
All Patients	–113.4 µm
Rescue-Free Patients	–132.7 µm

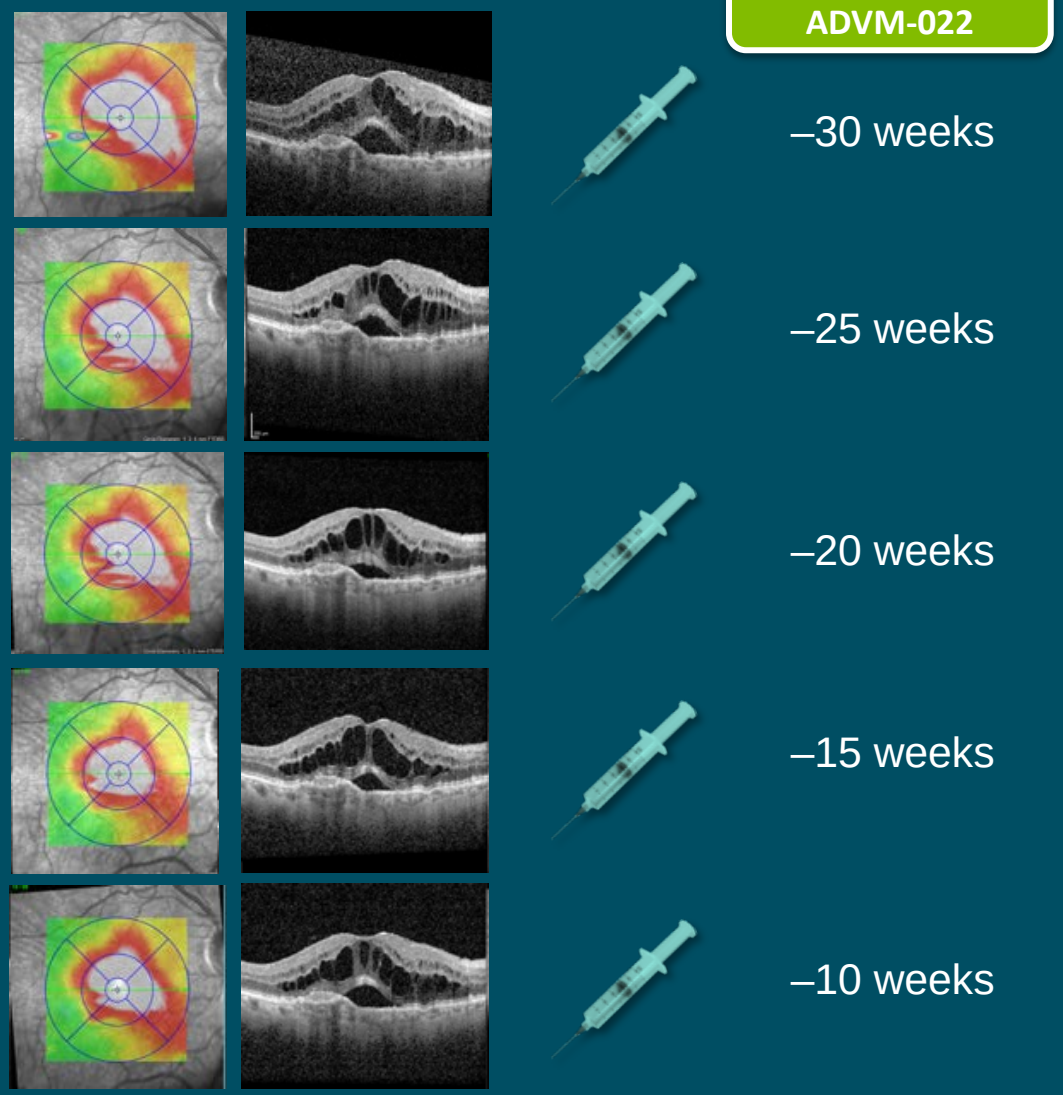
**N=8 for Week 4, 16 and 20; N=7 at Week 24*
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1)
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Case Study: Cohort 3, Subject 5

Persistent fluid despite frequent anti-VEGF injections

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



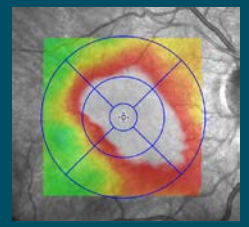
Aflibercept injections

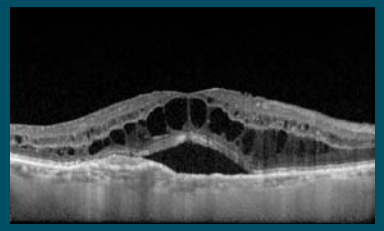
** Excluding the aflibercept injection received at the Screening visit*
IVT, intravitreal therapy; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor

Case Study: Cohort 3, Subject 5

Rapid and sustained anatomical improvements

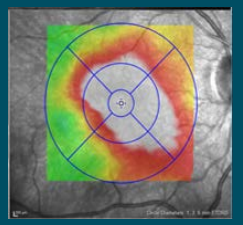
–3 weeks
Screening
BCVA: 77 letters
CST: 678 µm

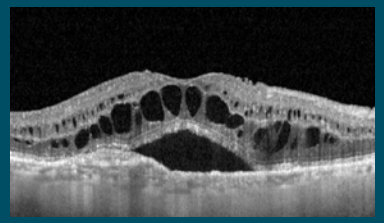




Aflibercept IVT

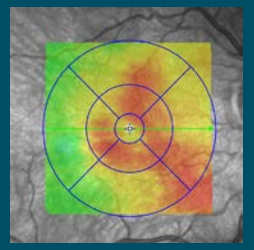
–2 weeks
BCVA: 75 letters
CST: 664 µm

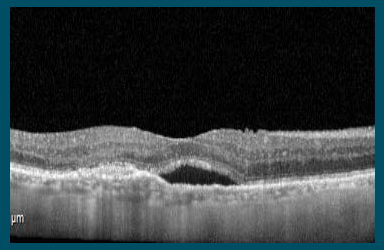




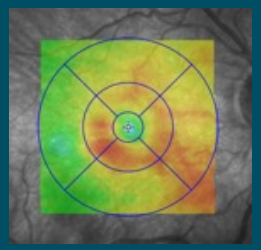
ADVM-022

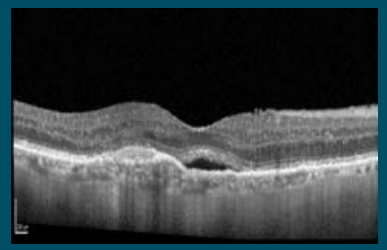
0 weeks
BCVA: 82 letters
CST: 355 µm



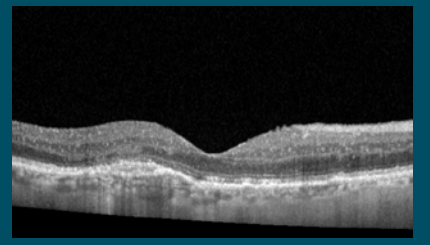


+1 week
BCVA: 80 letters
CST: 338 µm

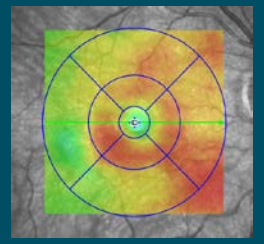


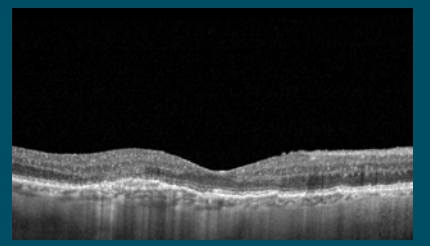


+12 weeks
BCVA: 81 letters
CST: 257 µm

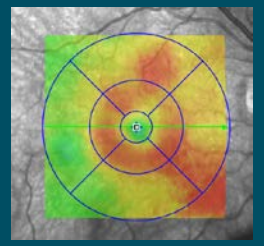


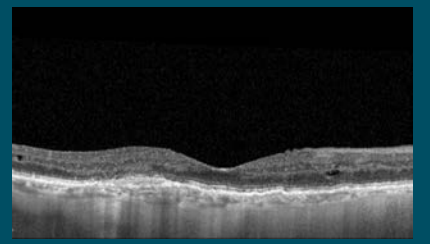
+24 weeks
BCVA: 83 letters
CST: 272 µm



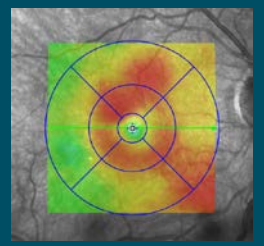


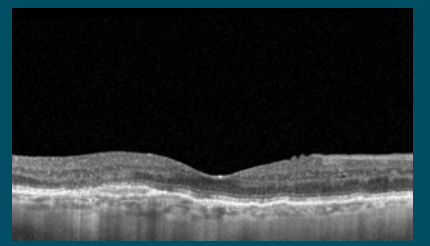
+36 weeks
BCVA: 83 letters
CST: 286 µm





+48 weeks
BCVA: 83 letters
CST: 300 µm





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

ADVM-022 Greatly Reduced anti-VEGF Injection Burden in wet AMD – Warrants Further Investigation in Larger Studies

- ADVM-022 continues to be well tolerated with a favorable safety profile at both high and low doses (n=30)
  - All ADVM-022-related ocular adverse events were mild (78%) to moderate (22%)
  - Ocular inflammation, when observed, has been responsive to steroid eye drops
- ADVM-022 continues to show robust and sustained efficacy at both high and low doses
  - Mean BCVA maintained
  - Mean CST maintained to improved
- Durability out to 92 weeks from a single IVT injection with zero supplemental injections in Cohort 1
- Robust aqueous anti-VEGF protein expression observed at 18 months in Cohort 1
- Substantial reduction in annualized anti-VEGF injection frequency following ADVM-022 in patients who previously required frequent injections to maintain vision:
  - High dose: 99% reduction
  - Low dose: 85% reduction
- Most patients are supplemental anti-VEGF injection free in OPTIC:
  - High dose: 14/15 patients injection free
  - Low dose: 10/15 patients injection free

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor; IVT, intravitreal *Data cut: Oct 15, 2020*

INFINITY: Phase 2 Trial of ADVM-022 in DME

Multi-center, randomized, double-masked, active comparator-controlled

INFINITY Gene Therapy in DME

- Evaluate a single IVT injection of ADVM-022 in patients with vision impairment due to center involving diabetic macular edema (DME)
- Designed to demonstrate superior disease control compared to a single aflibercept injection, measured by time to worsening of DME disease activity
- Additional objectives assess frequency of rescue aflibercept to the study eye, visual acuity (BCVA), retinal anatomy (OCT and DRSS) and safety outcomes

Day 1: Aflibercept/Sham

Day 8: ADVM-022/Sham

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

1. Loss of >5 letters in BCVA from best prior BCVA, due to worsening DME disease activity
2. Increase in central subfield thickness (CST) >50 µm from best prior CST

Screening and Randomization

Clinical assessments with rescue aflibercept from week 8

Weeks: 4 8 12 16 20 24 PE** 28 32 36 40 44 48 EOS***

Steroid eye drops prophylaxis*

Recent onset DME

R

Arm 1: ADVM-022 $6x10^{11}$ vg IVT

Arm 2: ADVM-022 $2x10^{11}$ vg IVT

Arm 3: Aflibercept 2 mg IVT

DRSS, Diabetic Retinopathy Severity Score
OCT, Optical Coherence Tomography
CST, Central Subfield Thickness

*All subjects receive a 7-week course of difluprednate eye drops, starting at QID and tapering to QD
**PE= Primary Endpoint assessment
***EOS= End of Study assessment

www.INFINITYclinicaltrial.com or
https://www.clinicaltrials.gov/ct2/show/NCT04418427

ADVM-022 Acknowledgments

Investigators, Study Teams and Participants

- David Boyer MD
- Brandon Busbee MD
- Carl Danzig, MD
- Brian Joondeph MD
- Arshad Khanani MD
- James Major MD
- Dante Pieramici MD
- Carl Regillo MD
- Charles Wykoff MD, PhD
- Mehdi Gasmi PhD
- Szilard Kiss MD
- Aaron Osborne MBBS
- Carol Hoang PharmD
- Adam Turpcu PhD
- Carol Chung PhD

Thank you