OPTIC Study of Intravitreal Gene Therapy With ADVM-022 for Neovascular Age-related Macular Degeneration

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- On behalf of the OPTIC Investigators -

OPTIC

Gene Therapy in nAMD

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Financial Disclosure

Presenter:

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C (Consultant): Adverum, Allergan, Apellis, Genentech, Kodiak Sciences, Regeneron, REGENXBIO

R (Recipient): Akorn, Bausch + Lomb Surgical

Key Learnings from OPTIC Trial in anti-VEGF Experienced nAMD Patients

OPTIC Gene Therapy in nAMD

- ADVM-022 provides durable, sustained efficacy observed with both doses (2×10^{11} vg/eye, 6×10^{11} vg/eye)
  - Patients maintained or gained vision (BCVA), stable to improved retinal anatomy (CST)
  - Aflibercept protein expression within targeted therapeutic range and stable out to 104 weeks
  - 85%-96% reduction in annualized injection frequency
- Well-tolerated safety profile
  - Lower ADVM-022-related ocular adverse events at 2×10^{11} vg/eye dose
  - Post prophylaxis inflammation at 2×10^{11} vg/eye dose is minimal and occurs in few patients
- Cohort 3 [2×10^{11} vg/eye] informative for Phase 3 dose selection
  - Efficacy (BCVA, CST), reduction in annualized injection frequency and aflibercept protein expression similar to 6×10^{11} vg/eye dose
  - Majority of patients did not require more than 6 weeks of prophylactic steroid eye drops
- Phase 3 trials of ADVM-022 in treatment naïve patients planned in 4Q21

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

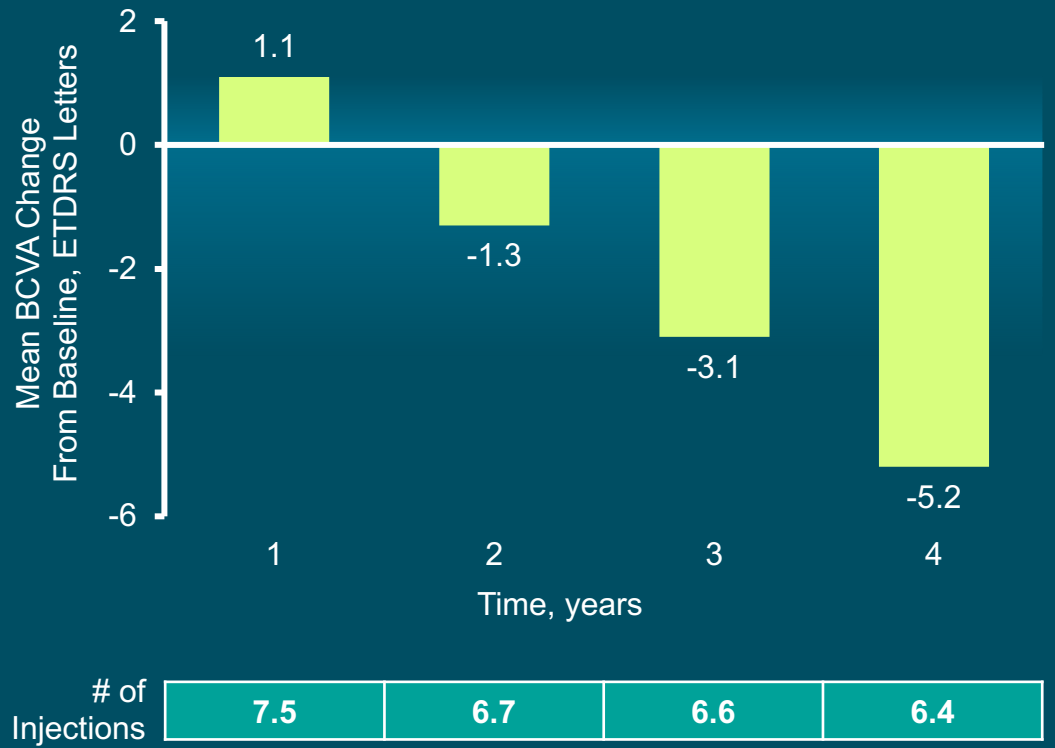
Data cut: March 10, 2021

Real-world anti-VEGF Patient Outcomes

Undertreatment leads to vision loss over time

OPTIC Gene Therapy in nAMD

98,821 Eyes from 79,885 US Patients Receiving Routine Intravitreal anti-VEGF Therapy



# of Injections	7.5	6.7	6.6	6.4

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. Ophthalmol Retina 2020;4:122–133

ADVM-022: 7m8 Adeno-Associated Virus Gene Therapy Vector

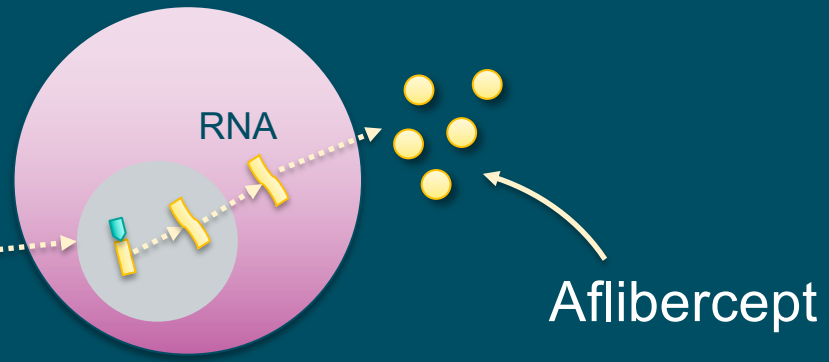
Designed for continuous delivery of aflibercept by intravitreal injection

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

Strong, Ubiquitous Promoter Designed for Robust Protein Expression



Target Retinal Cell Expresses Aflibercept

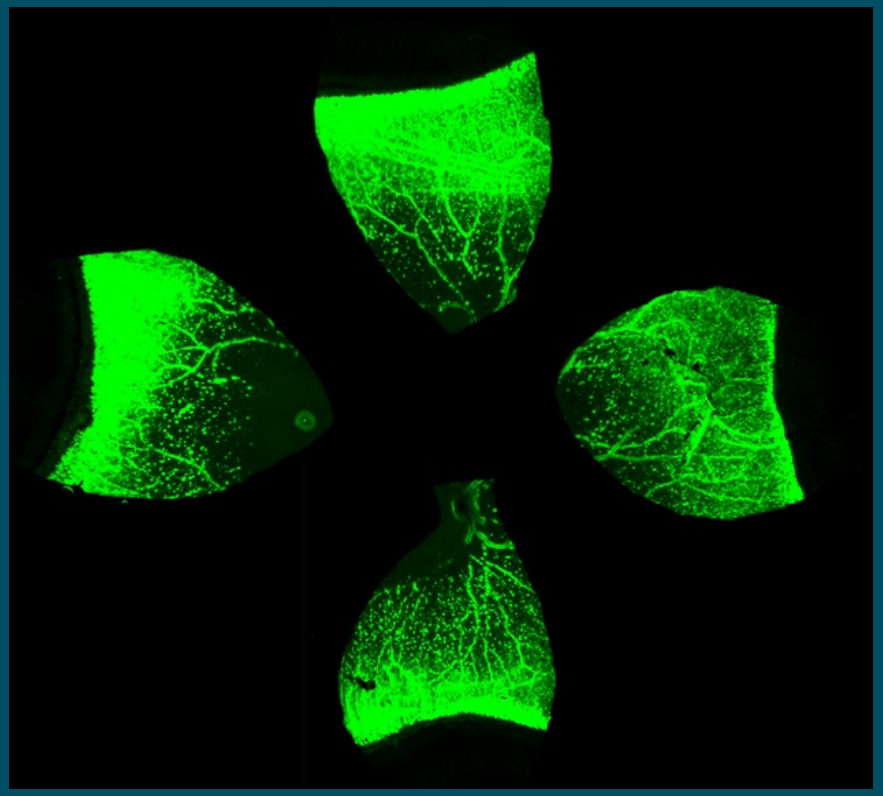
Codon-Optimized cDNA

IVT, intravitreal

Grishåanin, 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]

NHP, non-human primate

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

OPTIC Study: Evaluating ADVM-022 in Treatment Experienced Patients with nAMD

OPTIC
Gene Therapy in nAMD

Status

- 4 cohorts fully enrolled
- Follow-up to 104 weeks

Primary Objective

- Assess the safety and tolerability of a single IVT injection of ADVM-022

Secondary Objective

- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy

	Prophylaxis Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops**, 6wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6wks

Supplemental Aflibercept (2 mg IVT) Criteria:

1. Loss of ≥10 letters in BCVA (ETDRS) 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; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; SD-OCT, spectral domain optical coherence tomography; NCT03748784*

OPTIC Patient Status

	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	Completed (all with 104 weeks)	64–92 weeks (median 88)	48–72 weeks (median 68)	32–44 weeks (median 36)
Baseline Characteristics	✓	✓	✓	✓
Safety Data	✓	✓	✓	✓
Efficacy Data†	✓	✓	✓	✓
Aqueous anti-VEGF Protein Expression Data	✓	N/A	✓	✓

†Includes BCVA and CST outcomes and need for supplemental anti-VEGF injection

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Neovascular AMD Study Population Previously Required Frequent Injections to Maintain Vision

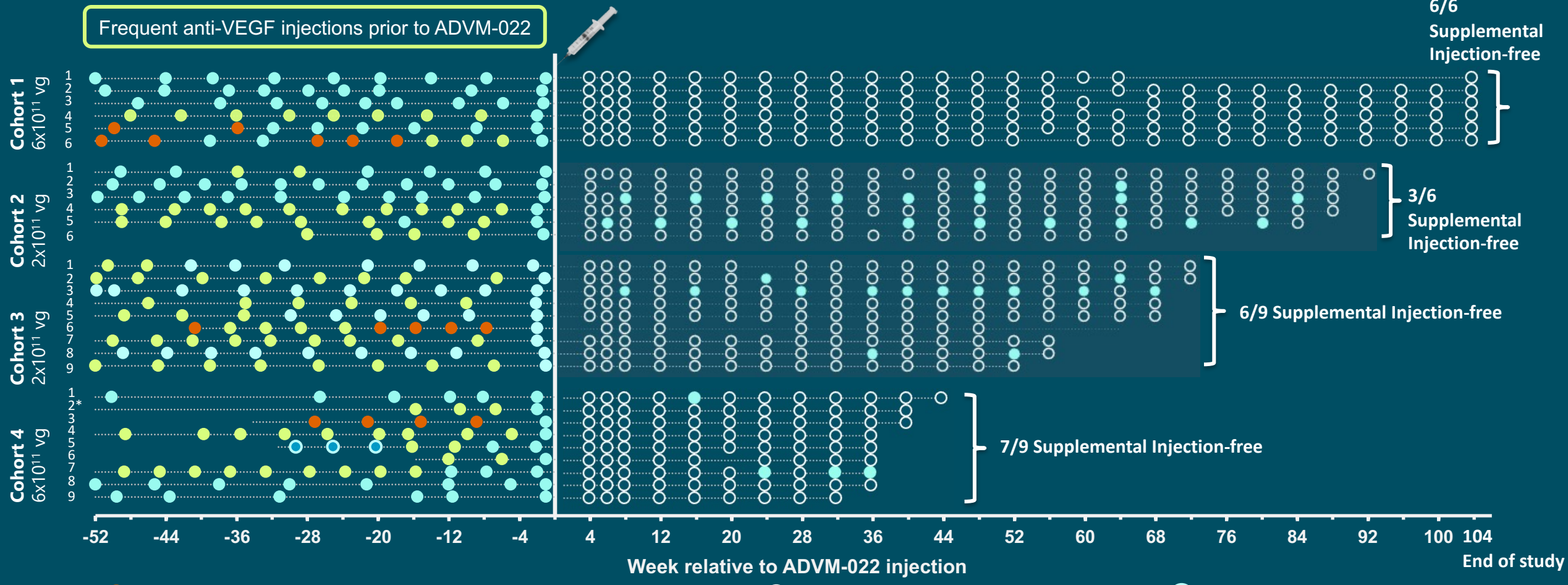
OPTIC Gene Therapy in nAMD

Baseline Characteristics	Cohort 1 6E11 (N=6)	Cohort 2 2E11 (N=6)	Cohort 3 2E11 (N=9)	Cohort 4 6E11 (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

Majority of Patients are Supplemental Injection Free after a Single IVT Injection of ADVM-022 in OPTIC

OPTIC Gene Therapy in nAMD



Five patients were diagnosed <1 year prior to ADVM-022 injection: one each in Cohorts 2 and 3, three in Cohort 4.
*Cohort 2, Patient 6 death due to lung malignancy; *Incomplete prior data for Cohort 4, Patient 2.*
***Received in a clinical trial not yet unmasked (NCT03790852).*
Cohort 4, Patient 4 had a port delivery system (PDS) implanted 3 years prior to Screening (explanted 1.5 years later).

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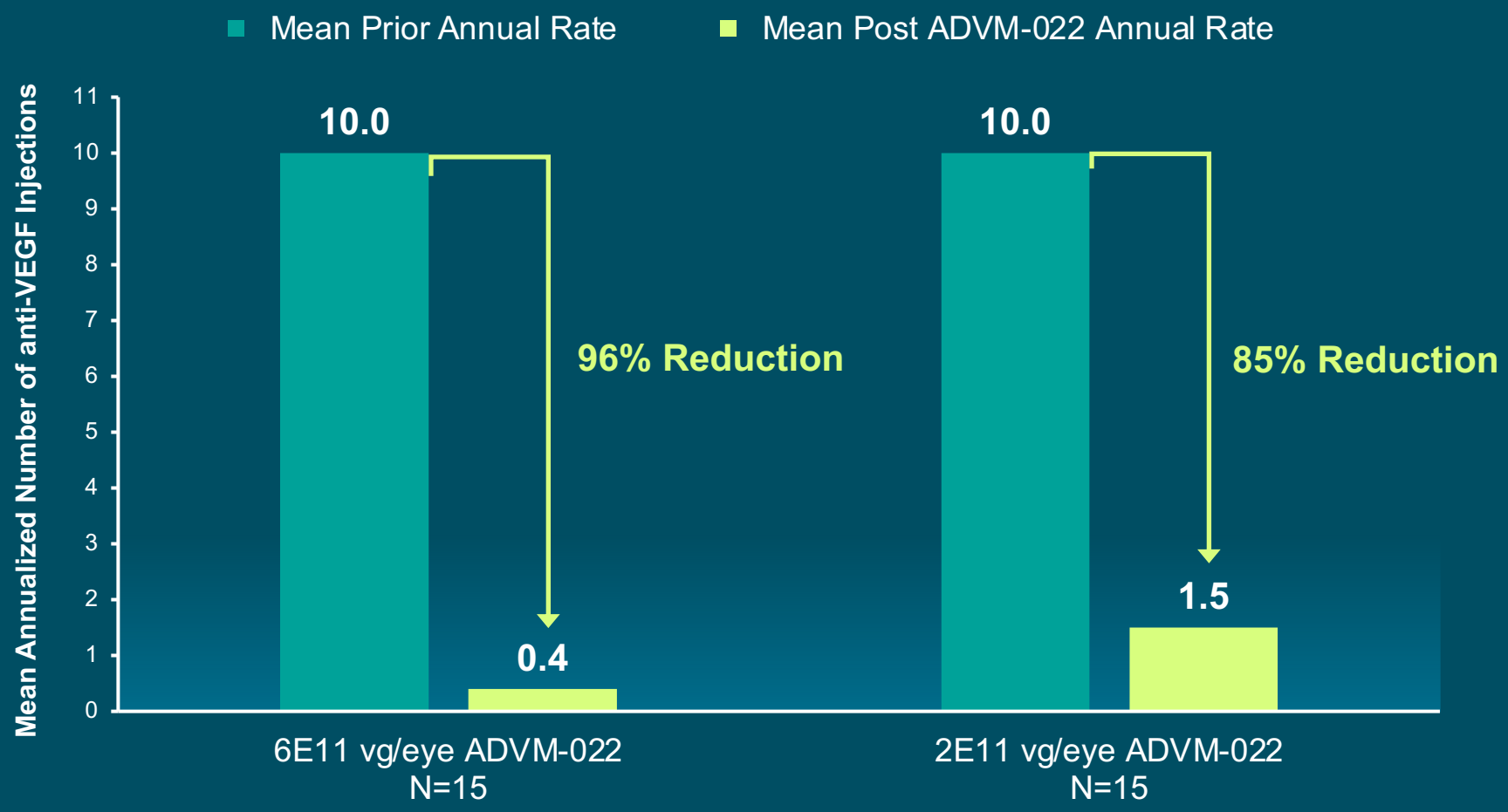
85%-96% Reduction in Annualized anti-VEGF Injection Following ADVM-022



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).

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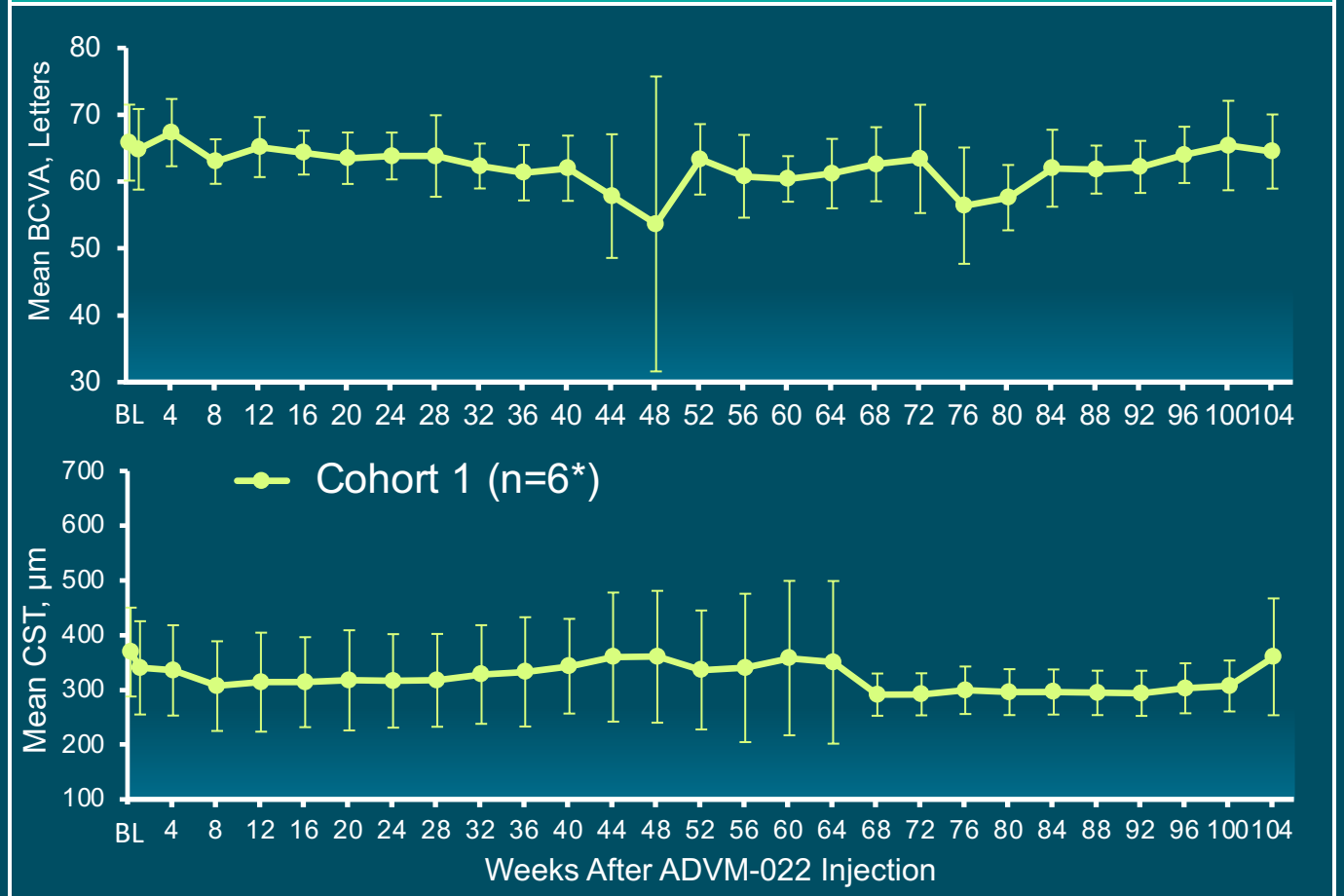
Cohort 1 [6E11]: BCVA and CST Stable, Zero Supplemental Injections

Mean (90% CI) by Visit Through Week 104



Latest Outcomes at Week 104

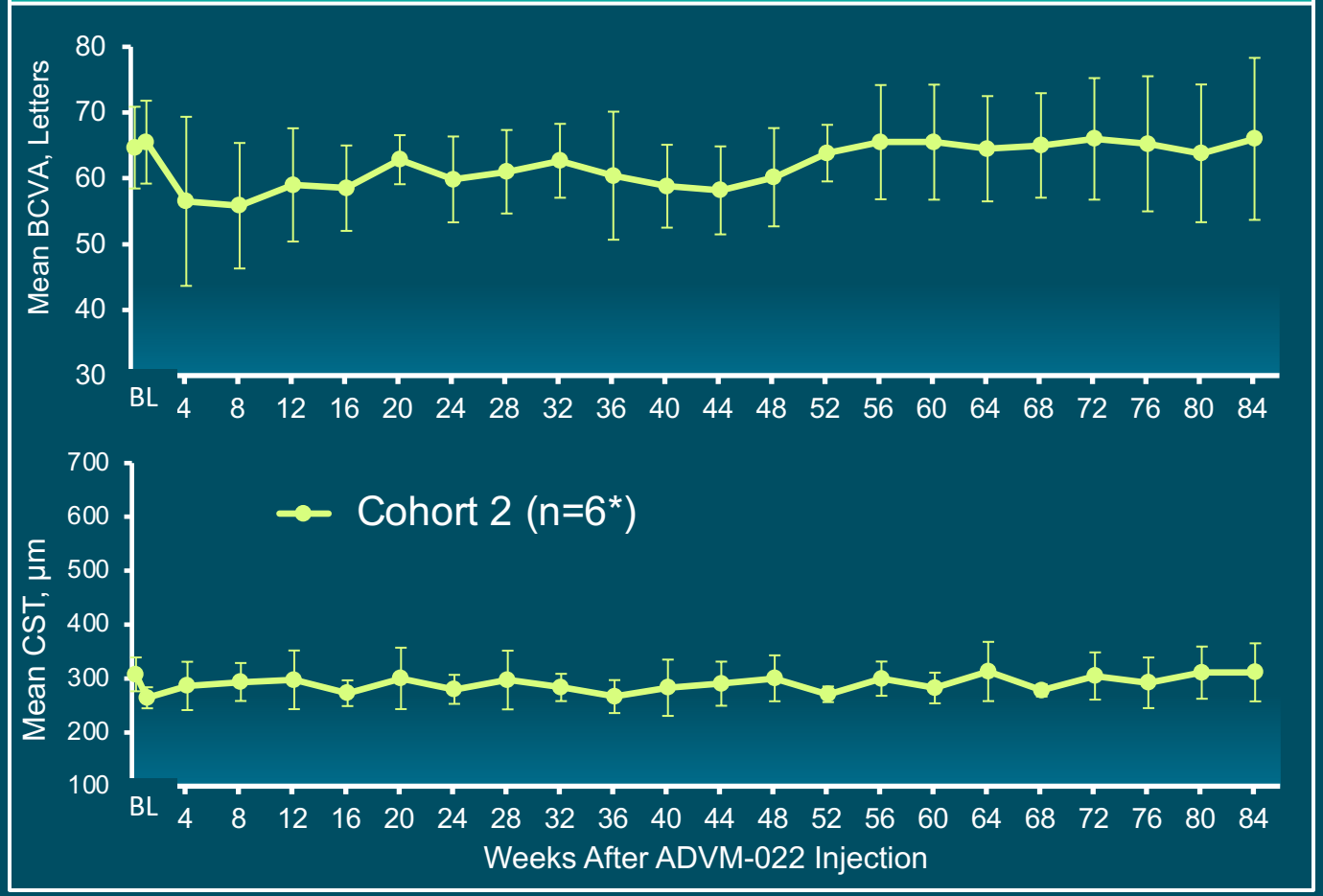
Follow-Up	All with 104 weeks (median 104)
Supplemental-Free Patients	100% (6/6)
Mean BCVA Change from Baseline	
All Patients	–1.3 Letters
Mean CST Change from Baseline	
All Patients	–8.7 µm

**One patient had low BCVA and no CST values at 44 and 48 weeks due to retinal detachment; n=5 from Week 56 to 100*
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
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Data cut: March 10, 2021

Cohort 2 [2E11]: BCVA and CST Maintained Over Time

Mean (90% CI) by Visit Through Week 84



Latest Outcomes (as of 3/10/2021)

Follow-Up	64**–92 weeks (median 88)
Supplemental-Free Patients	50% (3/6)
Mean BCVA Change from Baseline	
All Patients	–1.5 Letters
Supplemental-Free Patients	–1.0 Letters
Mean CST Change from Baseline	
All Patients	–28.2 µm
Supplemental-Free Patients	–30.3 µm

**n=5 for Week 36, 40, 68 to 84 visits (n=4 at Week 76).*
***A patient missed visits after Week 64 due to worsening of COPD and died of lung malignancy at ~76 weeks.*
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
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

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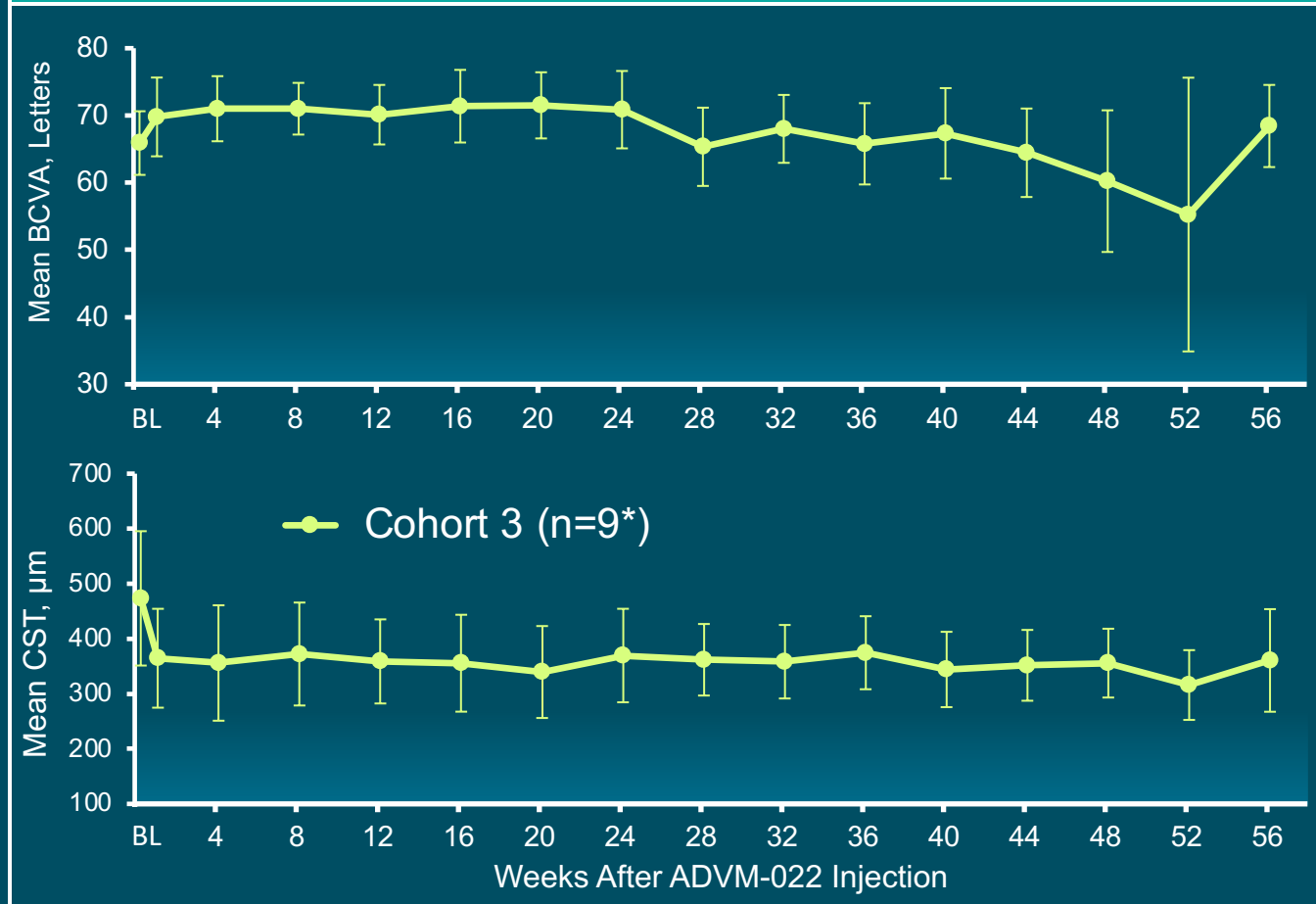
Cohort 3 [2E11]: BCVA Maintained and CST Improved

Mean (90% CI) by Visit Through Week 56



Latest Outcomes (as of 3/10/2021)

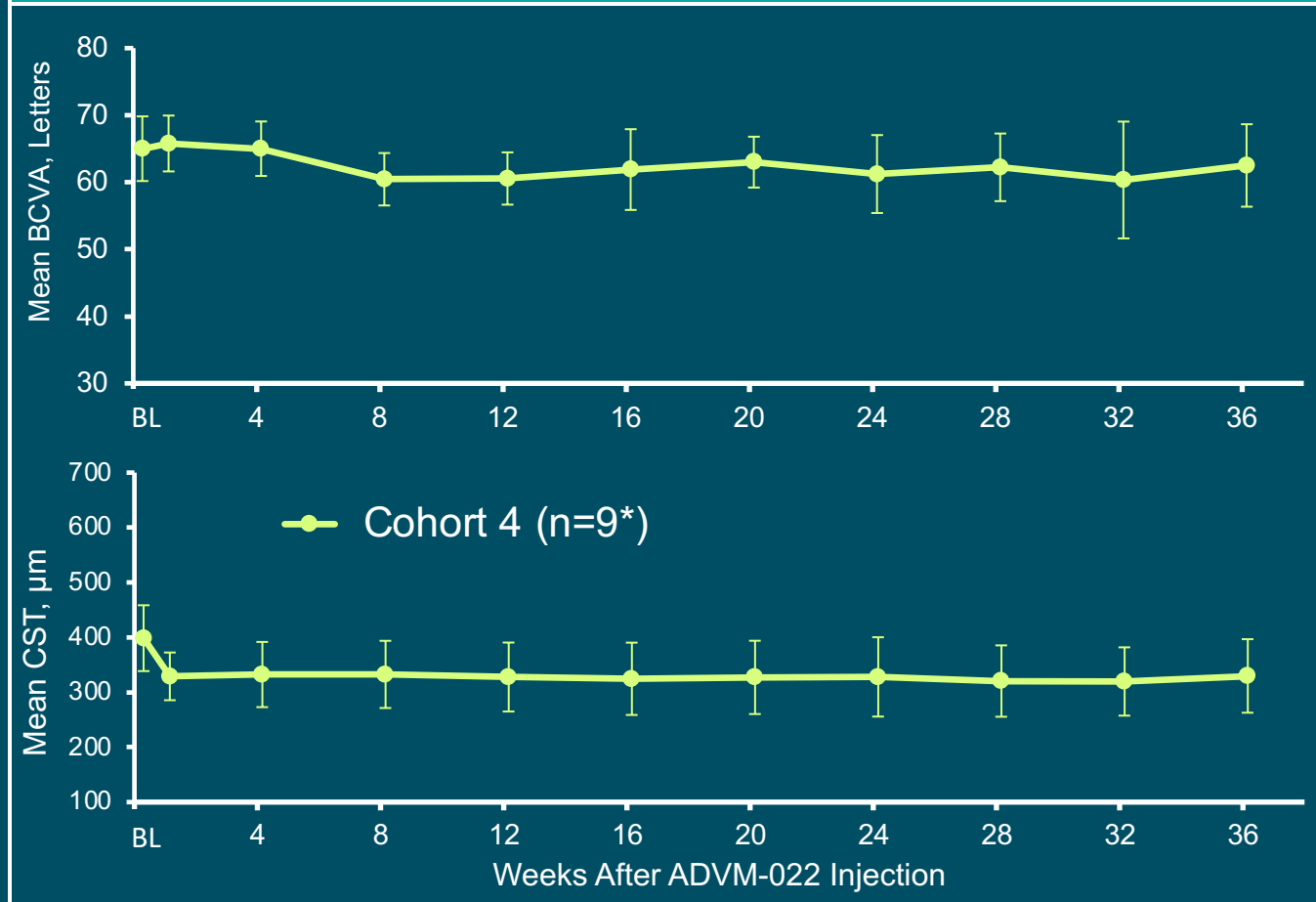
Follow-Up	48–72 weeks (median 68)
Supplemental-Free Patients	67% (6/9)
Mean BCVA Change from Baseline	
All Patients	+1.4 Letters
Supplemental-Free Patients	+4.3 Letters
Mean CST Change from Baseline	
All Patients	–134.4 µm
Supplemental-Free Patients	–181.7 µm

**n=8 for Week 4, 16 and 20; n=7 at Week 24; n=8 (BCVA) and 5 (CST) at Week 52; n=7 (BCVA) and 6 (CST) at Week 56.*
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
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Data cut: March 10, 2021

Cohort 4 [6E11]: BCVA and CST Maintained Over Time

Mean (90% CI) by Visit Through Week 36



Latest Outcomes (as of 3/10/2021)

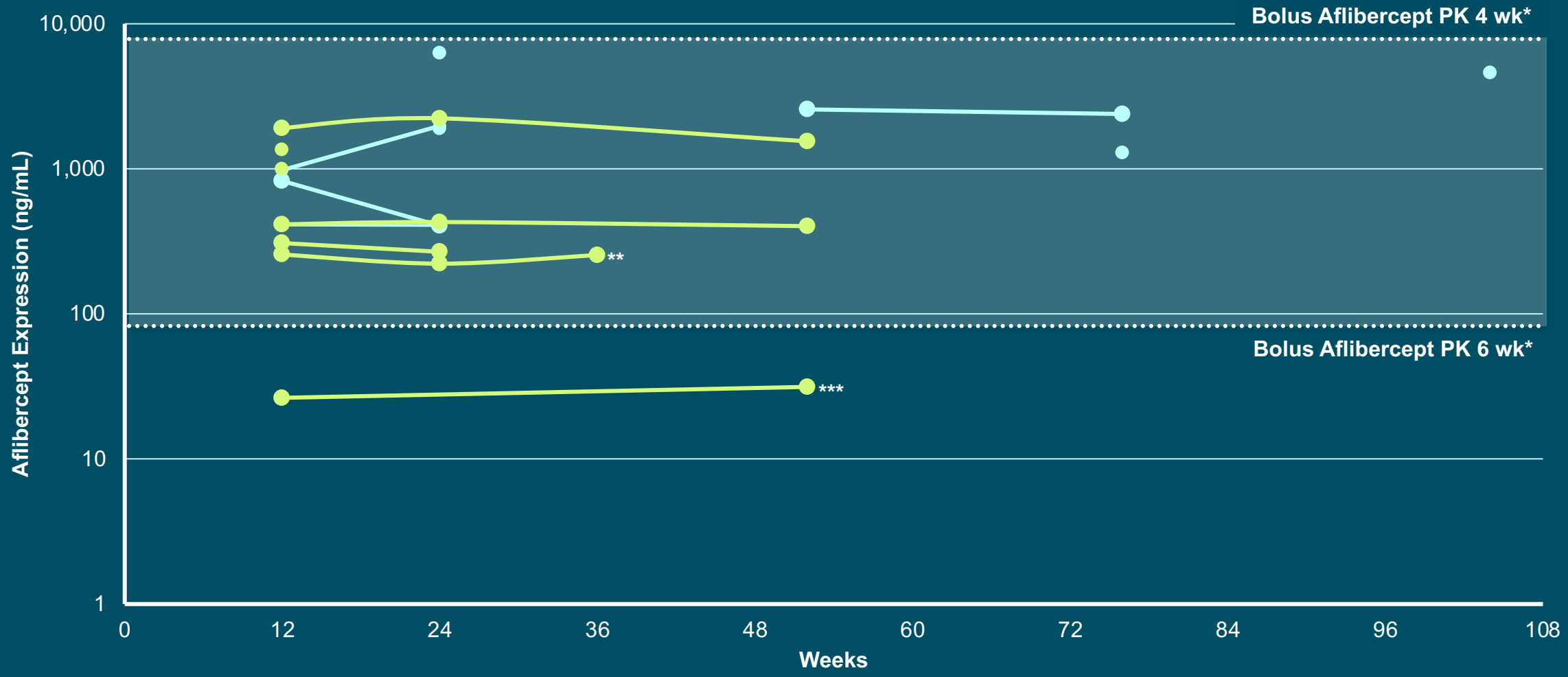
Follow-Up	32–44 weeks (median 36)
Supplemental-Free Patients	78% (7/9)
Mean BCVA Change from Baseline	
All Patients	–0.2 Letters
Supplemental-Free Patients	–0.4 Letters
Mean CST Change from Baseline	
All Patients	–77.1 µm
Supplemental-Free Patients	–77.3 µm

**n=8 at Weeks 20 and 36*
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
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Data cut: March 10, 2021

Robust Aflibercept Expression Levels Observed for Both Doses

Within modeled therapeutic range, reaching top of dose response curve



**Modeled based on Do et al. Retina 2020; 40:643-647.*
*** Patient rescued at Week 36*
**** Patient rescued at Week 24. Sample collected 28 weeks after supplemental injection.*
Protocol amendment for aqueous sample collection for patients that consented. No samples available from Cohort 2.
To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

Data cut: March 10, 2021

Safety Summary Across Cohorts

- No ADVM-022-related non-ocular adverse events
  - A patient (Cohort 2) died of lung malignancy ~76 weeks
- Inflammation when observed is mild and responsive to steroid eye drops
  - Immune response occurs early and is well controlled with steroid eye drops
  - Ocular inflammation is minimal at 2×10^{11} vg/eye dose and is responsive to 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 (80%) to moderate (20%)
  - 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

Data cut: March 10, 2021

Adverse Events Across Cohorts

ADVM-022 related events were mild (80%) or moderate (20%)

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	32	5	21	5	15	8	32
	Total Ocular	6	57	6	37	8	37	8	43
Non-Ocular†	Serious ‡	1	1	2	5	2	2	0	0
	Total Non-Ocular†	5	20	6	14	6	12	3	4

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

*** ADVM-022 related ocular events were mild (80%) or moderate (20%)*

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

‡Serious non-ocular AEs included lumbar spinal stenosis (1) in Cohort 1; COPD (1), pneumonia (1, fatal), lung neoplasm malignant (1), pneumothorax (1), and hypertensive emergency (1) in Cohort 2; and COPD exacerbation (1), and stable angina pectoris (1) in Cohort 3

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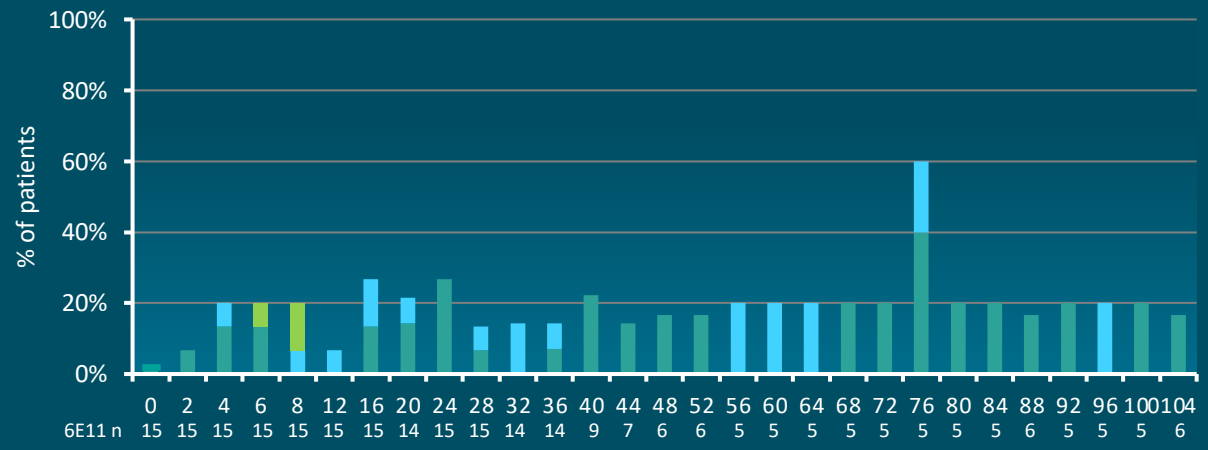
Lower Immune Response with 2×10^{11} vg/eye dose

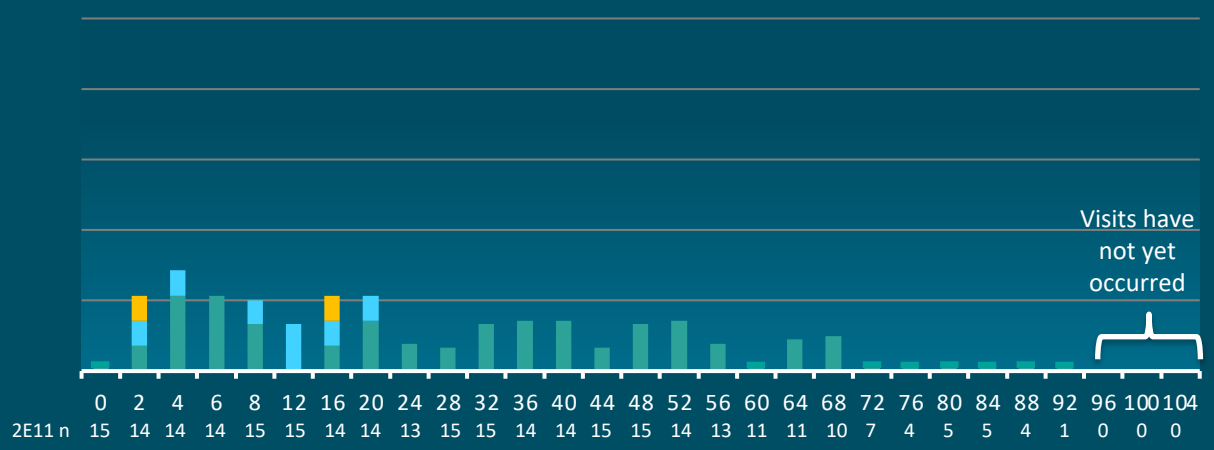
Frequency and severity of inflammation decreases over time

Cell Grades 0.5+ 1+ 2+ 3+ 4+

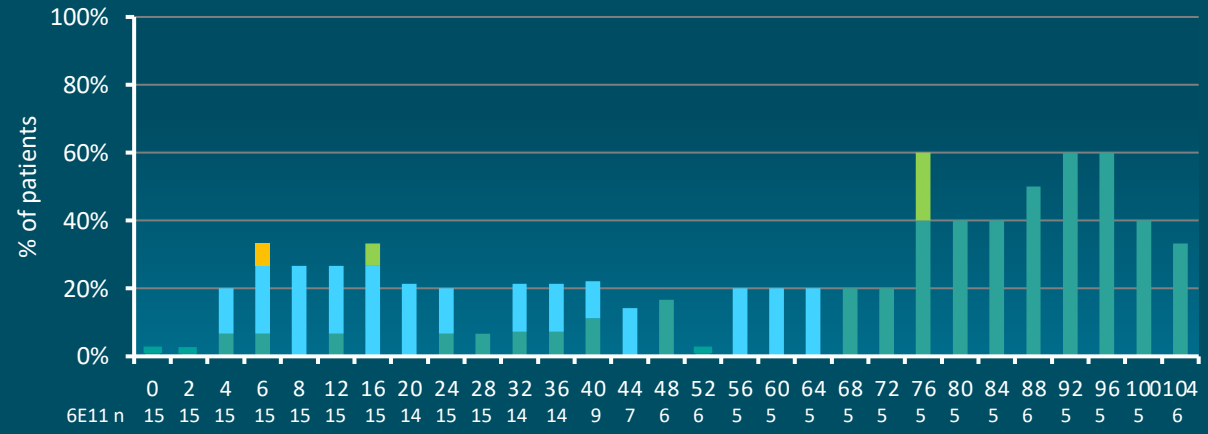
AC Cells (6×10^{11} vg/eye); Cohort 1 & 4



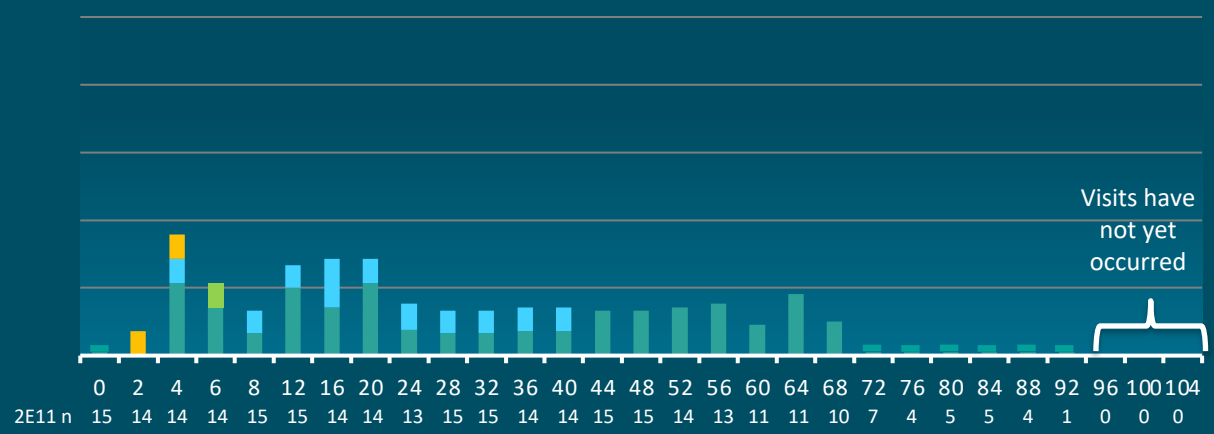
AC Cells (2×10^{11} vg/eye); Cohort 2 & 3



VC Cells (6×10^{11} vg/eye); Cohort 1 & 4



VC Cells (2×10^{11} vg/eye); Cohort 2 & 3



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 (AC): 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells
Vitreous cells (VC): 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 cut: March 10, 2021

AC – Inflammation was Mild and Decreasing Over Time in Cohort 3 *[2×10^{11} vg/eye dose, 6-week steroid drops prophylaxis]*

OPTIC Gene Therapy in nAMD

	Week																		
Patients		0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
	C3-1	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0
	C3-2	0	0	0	0	0	0	0	0	0.5	0	0	0	0	0	0	0	0	0	0
	C3-3*	0	0.5	0	1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5*	0	0.5	0.5	
	C3-4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	C3-5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	C3-6	0	-	0	0	-	-	-	0	0	0	0	0	0	-	-	-	-		
	C3-7**	0	0	0.5	0	0.5	0	0	0	0	0	0	0	0	0	0**				
	C3-8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
	C3-9	0	0	0	0	0	0	0	0	0	0	0	0	0	0					

*Cataract surgery before Week 56

**Cataract surgery before Week 56

AC Grade — 0 — 0.5+ — 1+ — 2+ — 3+ — 4+

Cell grades as assessed by slit lamp

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Data cut: March 10, 2021

VC – Inflammation was Mild and Decreasing Over Time in Cohort 3 *[2×10^{11} vg/eye dose, 6-week steroid drops prophylaxis]*

Patients	Week																		
	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
C3-1	0	0.5	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0
C3-2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C3-3*	0	0.5	0	0.5	0.5	0.5	0	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5*	0	0.5	0.5	
C3-4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
C3-5	0	1	0.5	0.5	0.5	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	
C3-6	0	-	0	0	-	-	-	0	0	0	0	0	0	-	-	-	-		
C3-7**	0	0	0	0	1	0.5	0	0	0	0	0	0	0	0	0**				
C3-8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
C3-9	0	0	0	0	0	0	0	0	0	0	0	0	0	0					

*Cataract surgery before Week 56

**Cataract surgery before Week 56

VC Grade — 0 — 0.5+ — 1+ — 2+ — 3+ — 4+

Cell grades as assessed by slit lamp

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Steroid Eye Drops Post Prophylaxis Decrease Over Time in Cohort 3 *[2×10^{11} vg/eye dose, 6-week steroid drops prophylaxis]*

OPTIC Gene Therapy in nAMD

6-week prophylaxis steroid eye drops

Patients	Week 0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
C3-1	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C3-2	4	2	0	0	0	0	0	0	2	3	3	3	0	0	0	0	0	0	0
C3-3*	4	3	2	4	2	4	4	4	4	4	4	4	4	4	4*	3	3	2	
C3-4	4	2	0	0	0	0	2	2	2	0	0	0	0	0	0	0	0	0	
C3-5	4	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
C3-6	4	2	0	0	0	0	0	0	0	0	0	0	0						
C3-7**	4	2	2	1	4	4	3	3	1	1	1	0.5	0.5	0.5	1**				
C3-8	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0				
C3-9	4	2	0	0	0	0	0	0	0	0	0	0	0	0					

*Cataract surgery before Week 56
**Cataract surgery before Week 56
0.5 represents drops every other day

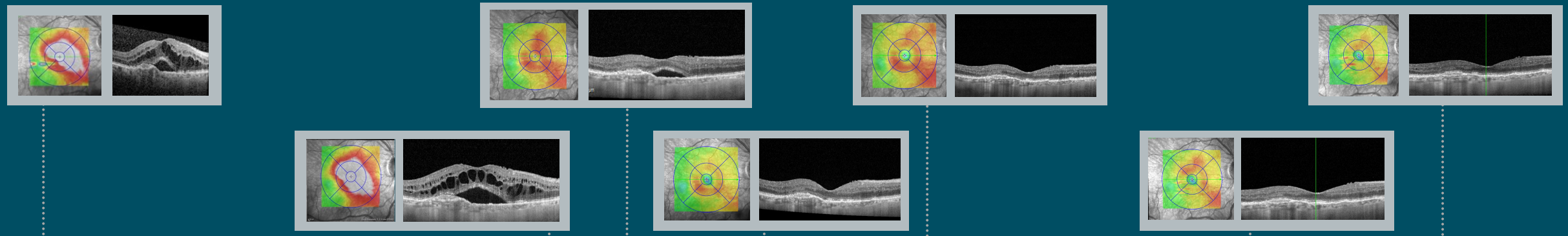
# of daily drops — 0 — 0.5 — 1 — 2 — 3 — 4

Data cut: March 10, 2021

Rapid and Sustained Improvements to Ocular Anatomy and Vision after Single IVT Injection of ADVM-022 [2E11]

OPTIC Gene Therapy in nAMD

Patient Case from Cohort 3 [2E11]: 82-year-old male with 19 IVTs prior to study with 9 IVTs in the last 12 months



Persistent fluid despite frequent anti-VEGF injections

-30 wks

-2 wks
BCVA: 75 letters
CST: 664 µm

Day 0
ADVM-022

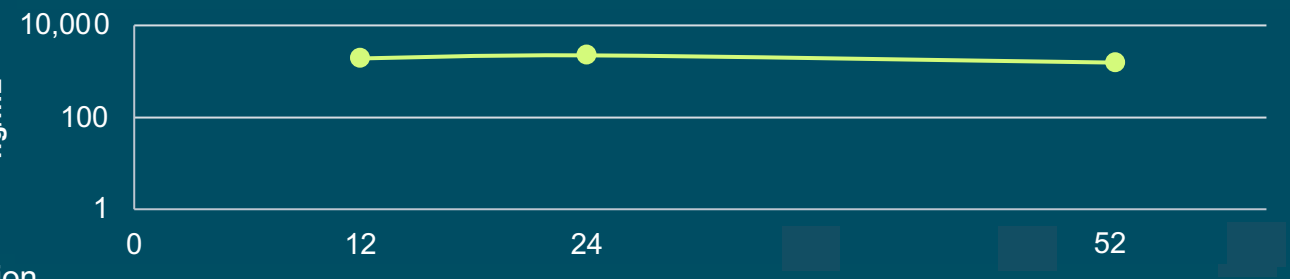
+12 wks
BCVA: 81 letters
CST: 257 µm

+24 wks
BCVA: 83 letters
CST: 272 µm

+52 wks
BCVA: 83 letters
CST: 281 µm

+68 wks
BCVA: 84 letters
CST: 281 µm

Treatment with aflibercept Q5W



Data cut: March 10, 2021

Key Learnings from OPTIC Study Sets the Direction for Accelerated Global Phase 3 Trials

OPTIC Gene Therapy in nAMD

- ADVM-022 provides durable, sustained efficacy observed with both doses (2×10^{11} vg/eye, 6×10^{11} vg/eye)
  - Patients maintained or gained vision (BCVA), stable to improved retinal anatomy (CST)
  - Aflibercept protein expression within targeted therapeutic range and stable out to 104 weeks
  - 85%-96% reduction in annualized injection frequency
- Well-tolerated safety profile
  - Lower ADVM-022-related ocular adverse events at 2×10^{11} vg/eye dose
  - Post prophylaxis inflammation at 2×10^{11} vg/eye dose is minimal and occurs in few patients
- Cohort 3 [2×10^{11} vg/eye] informative for Phase 3 dose selection
  - Efficacy (BCVA, CST), reduction in annualized injection frequency and aflibercept protein expression similar to 6×10^{11} vg/eye dose
  - Majority of patients did not require more than 6 weeks of prophylactic steroid eye drops
- Global Phase 3 trials of ADVM-022 in treatment naïve patients planned in 4Q21

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

Data cut: March 10, 2021

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