ADVM-022 Intravitreal Gene Therapy for Neovascular AMD – Phase 1 OPTIC Study

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- On behalf of the OPTIC Investigators -

OPTIC
Gene Therapy in nAMD

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Disclosures

- Consultant: 4DMT, **Adverum**, Aerpio, Allergan, Broadwing Bio, Dutch Ophthalmic Research Center, Genentech, Iveric bio, Kato Pharmaceuticals, Kodiak Sciences Inc., Novartis, Gemini Therapeutics, Graybug, Gyroscope, Nanoscope, Opthea, Oxurion, PolyPhotonix, Recens Medical, Regenxbio
- Research support: **Adverum**, Alkahest, Allergan, Gemini Therapeutics, Genentech, Graybug Gyroscope, Iveric Bio, NGM pharmaceuticals, Kodiak Sciences Inc., Novartis, Opthea, Ophthotech, Oxurion, Regenxbio; Recens Medical
- Speaker: Allergan, Genentech and Novartis

OPTIC Study Evaluated ADVM-022 in Treatment Experienced Patients with Neovascular AMD

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. AMD, age-related macular degeneration; 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	Completed (all with 2 years)	Completed‡ (median 2 years)	72–90 weeks (median 88)	52–64 weeks (median 56)
3-year extension study	✓	✓	November 2021	April 2022
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; ‡64–104 weeks of follow-up.

Data cut: July 16, 2021

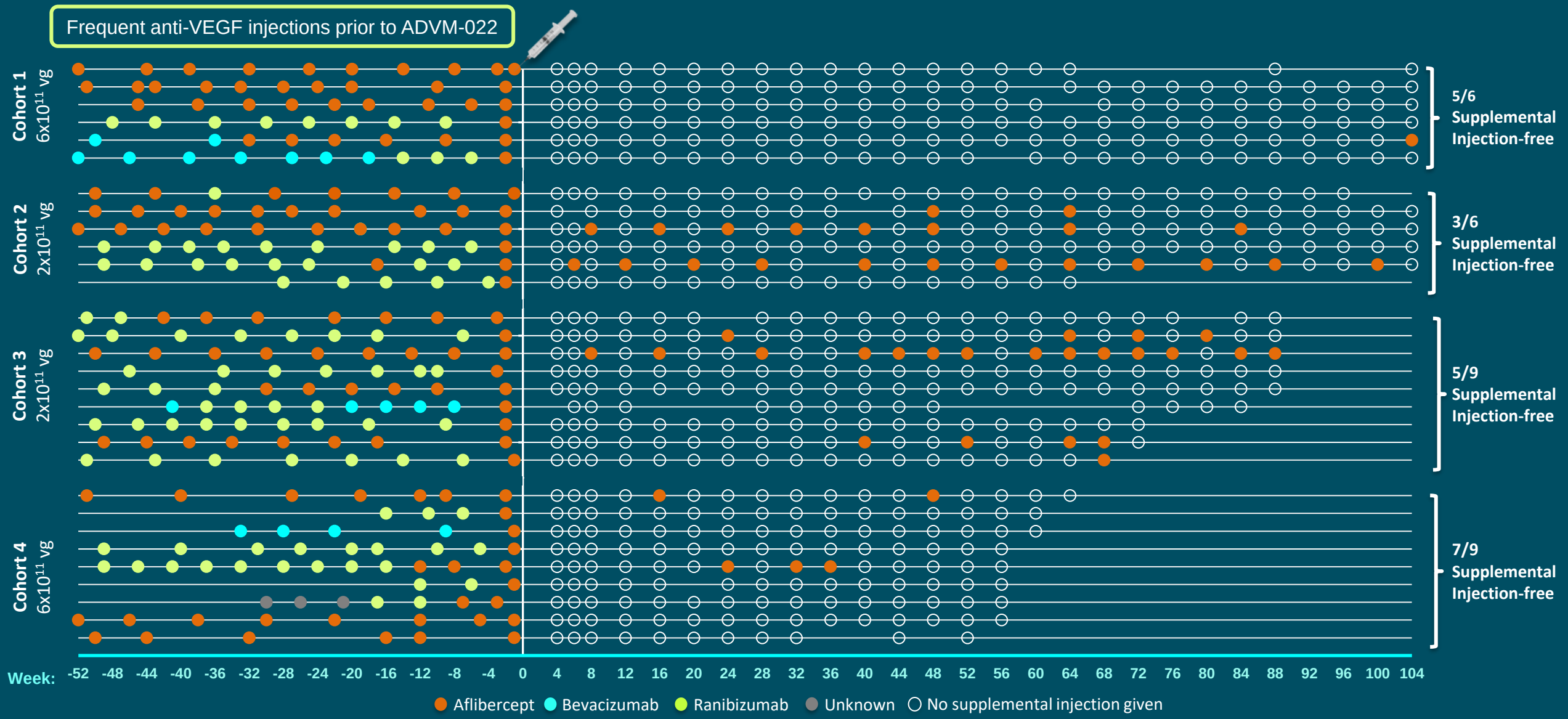
Neovascular AMD Study Population Previously Required Frequent Injections to Maintain Vision

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 (6–11)	8.9 (7–10)	6.6 (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



Six patients were diagnosed <1 year prior to ADVM-022 injection: one each in Cohorts 1, 2 and 3, three in Cohort 4. Cohort 2, Patient 1 death due to cardiopulmonary arrest due to hypoxia; *Cohort 2, Patient 6 death due to lung malignancy; Incomplete prior data for Cohort 4, Patient 2. Cohort 4, Patient 4 had a port delivery system (PDS) implanted 3 years prior to Screening (explanted 1.5 years later); Cohort 4, Patient 5 received in a clinical trial not yet unmasked (NCT03790852); IVT, intravitreal injection.*

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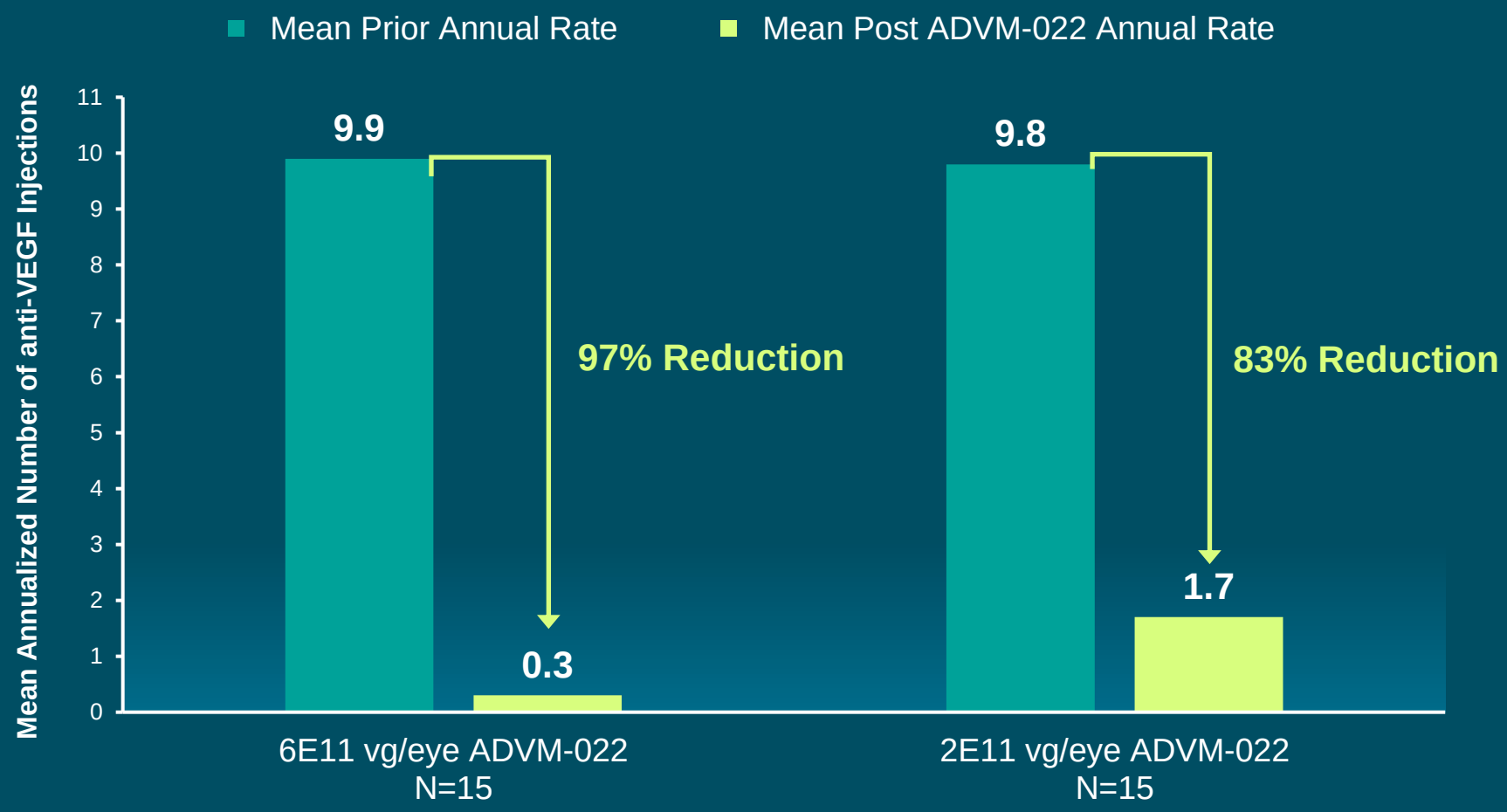
>80% Reduction in Annualized Anti-VEGF Injections Observed Following 2E11 ADVM-022 IVT Injection



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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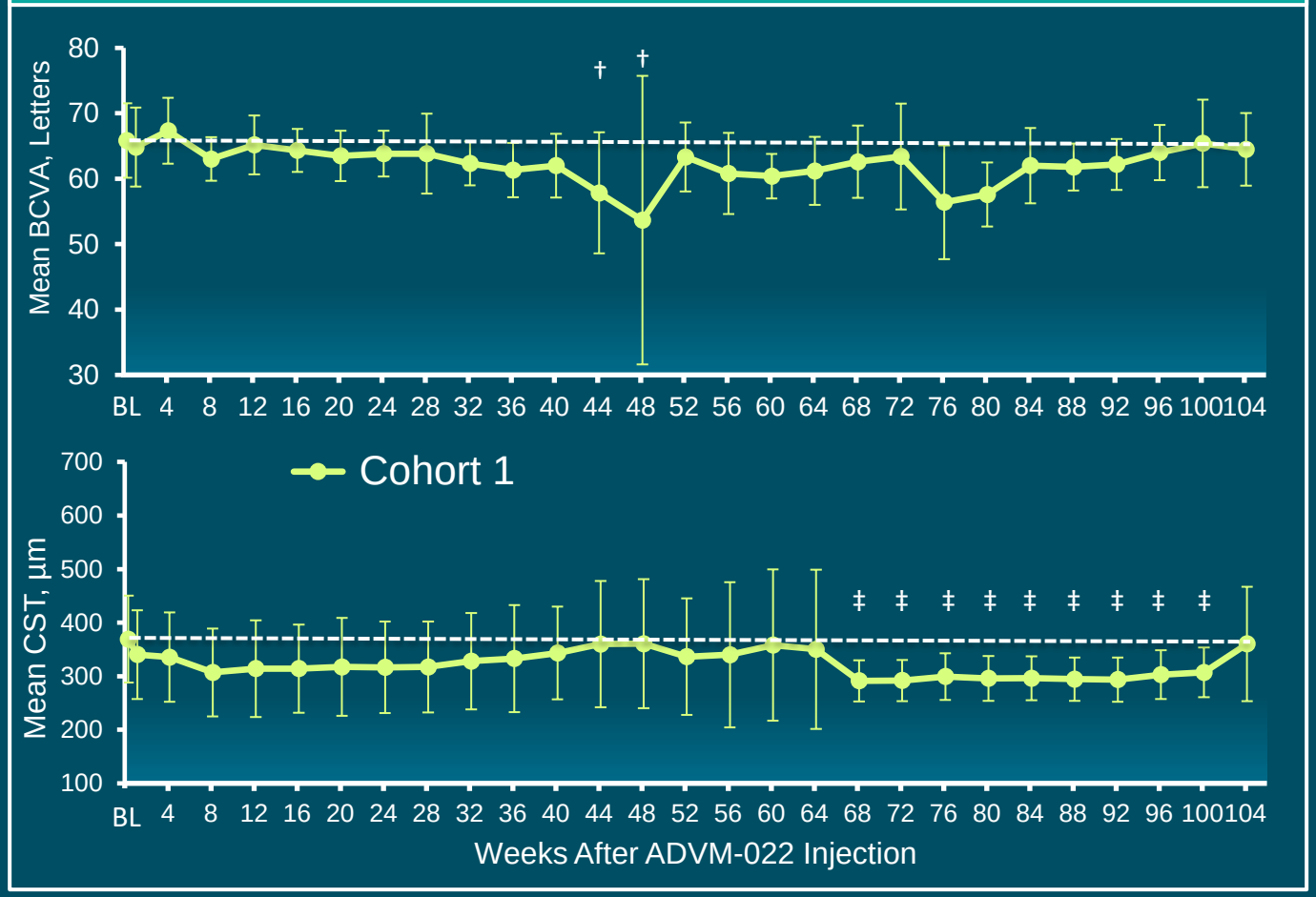
BCVA and CST Maintained Over Time in Cohort 1 [6E11]

Mean (90% CI) by Visit Through Week 104 (n=6)



Latest Outcomes at Week 104

Follow-Up	All with 104 weeks (median 104)
Mean BCVA Change from Baseline	–1.3 Letters
Mean CST Change from Baseline	–8.7 µm

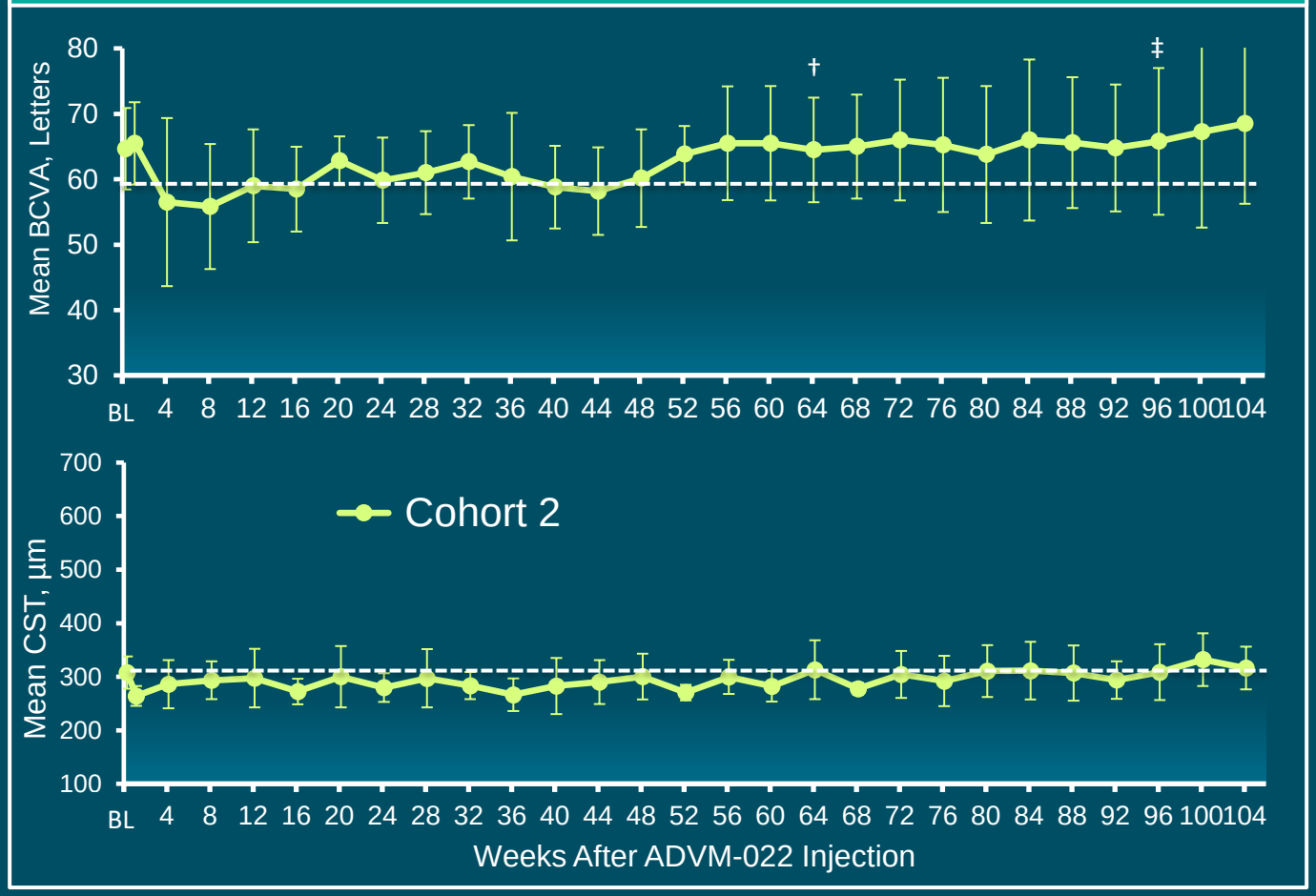
†One patient had low BCVA and no CST values at 44 and 48 weeks due to retinal detachment; ‡One patient who had a large PED missed their visits from week 68 through 100 because they had to stay remote due to COVID-19
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1);
BCVA, best corrected visual acuity; BL, baseline; CST, central subfield thickness; PED, pigment epithelial detachment.
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution.

-------- Denotes baseline

Data cut: July 16, 2021

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

Mean (90% CI) by Visit Through Week 104 (n=6)



Latest Outcomes (as of 7/16/2021)

Follow-Up	64–104 weeks (median 104)
Mean BCVA Change from Baseline	–0.8 Letters
Mean CST Change from Baseline	–15.5 µm

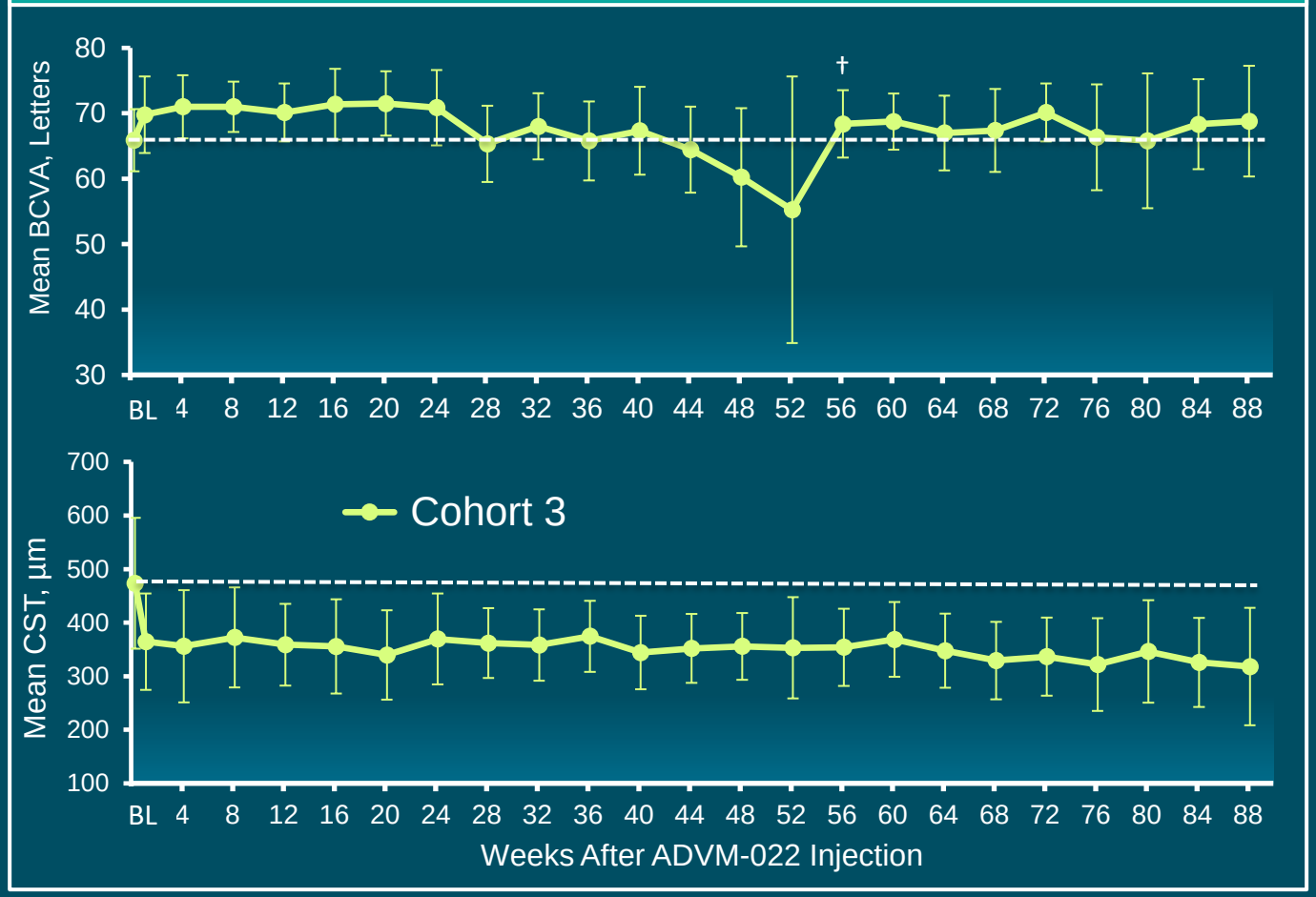
†A patient missed visits after Week 64 due to worsening of COPD and died of lung malignancy at ~76 weeks; ‡A patient died of a cardiopulmonary arrest due to hypoxia ~96 weeks
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1).
BCVA, best corrected visual acuity; BL, baseline; CST, central subfield thickness
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution.

-------- Denotes baseline

Data cut: July 16, 2021

BCVA Maintained and CST Improved Over Time in Cohort 3 [2E11]

Mean (90% CI) by Visit Through Week 88 (n=9)



Latest Outcomes (as of 7/16/2021)

Follow-Up	72–90 weeks (median 88)
Mean BCVA Change from Baseline	+2.6 Letters
Mean CST Change from Baseline	–142.3 µm

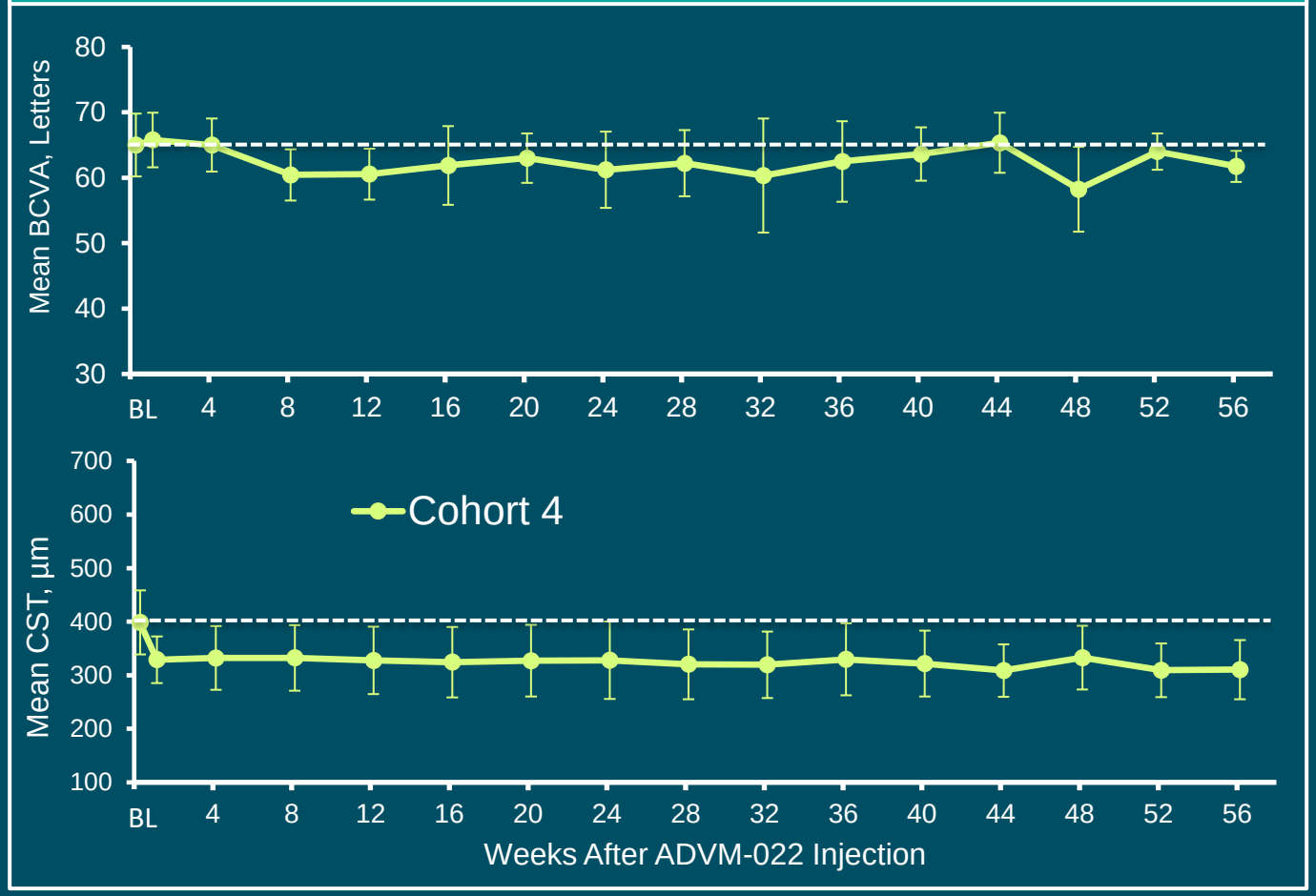
†2 patients had cataract surgery prior to week 56
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1)
BCVA, best corrected visual acuity; BL, baseline; CST, central subfield thickness
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution.

-------- Denotes baseline

Data cut: July 16, 2021

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

Mean (90% CI) by Visit Through Week 56 (n=9)



Latest Outcomes (as of 7/16/2021)

Follow-Up	52–64 weeks (median 56)
Mean BCVA Change from Baseline	–2.8 Letters
Mean CST Change from Baseline	–91.6 µm

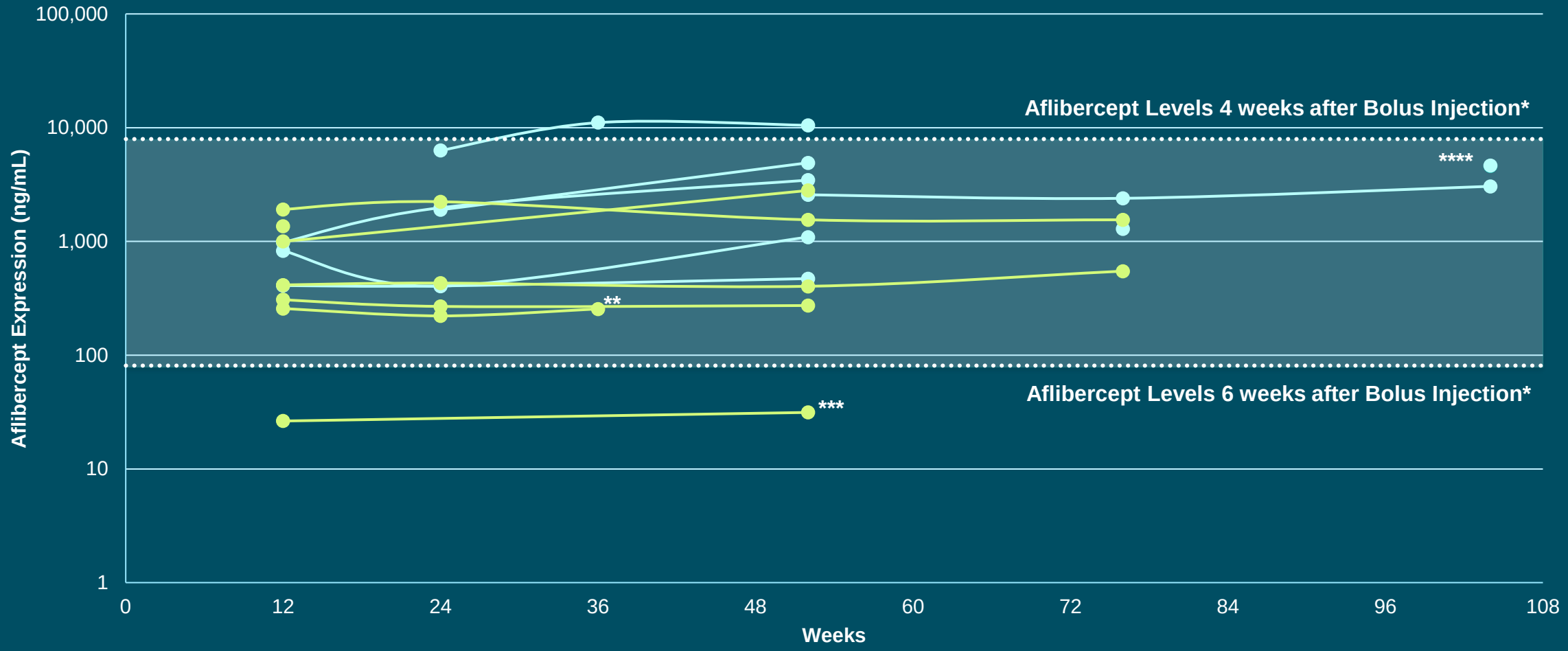
-------- Denotes baseline

Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1)
BCVA, best corrected visual acuity; BL, baseline; CST, central subfield thickness
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distributionort.

Data cut: July 16, 2021

Robust, Sustained Aflibercept Expression Levels Observed for Both Doses (N=11)

Within modeled aflibercept pharmacokinetic range post single Aflibercept 2mg at 4- and 6-weeks dosing



*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.
****Patient consented to aqueous sample collection at Week 104.
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.

6×10^{11} vg/eye Dose

2×10^{11} vg/eye Dose

Data cut: July 16, 2021

Safety Summary Across Cohorts

- No ADVM-022-related non-ocular adverse events
  - 2 patients (Cohort 2) died in the study
    - One patient died of lung malignancy ~76 weeks
    - One patient died of a cardiopulmonary arrest due to hypoxia ~96 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
- No clinically relevant low IOP events observed at either dose
- All ADVM-022-related ocular AEs were mild (83%) to moderate (17%)
  - One AE 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)

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

Data cut: July 16, 2021

ADVM-022 related events were Mild (81%) or Moderate (19%) Across All Cohorts

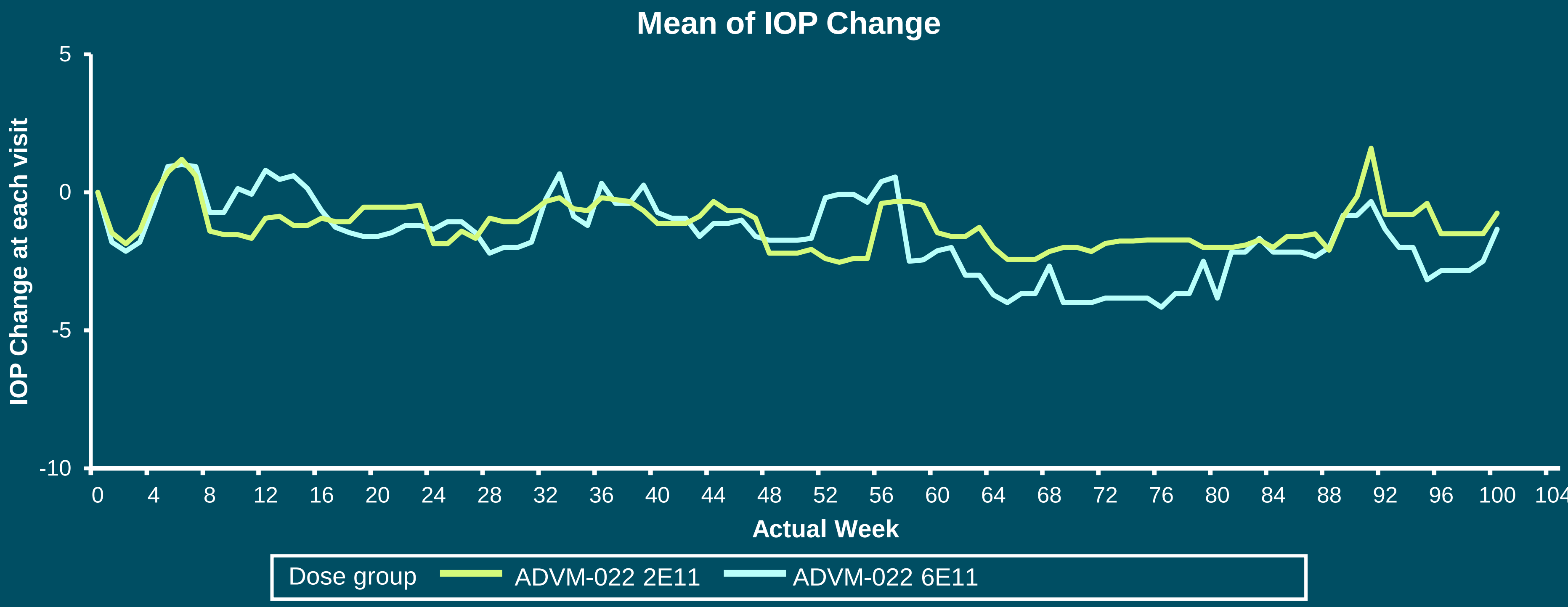
Adverse Events		Cohort 1 (N=6) 6×10^{11} vg/eye Oral steroids 13-day prophylaxis		Cohort 2 (N=6) 2×10^{11} vg/eye Oral steroids 13-day prophylaxis		Cohort 3 (N=9) 2×10^{11} vg/eye Steroid eye drops 6-week prophylaxis		Cohort 4 (N=9) 6×10^{11} vg/eye Steroid eye drops 6-week prophylaxis	
		Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ocular	Serious	2	2*	0	0	0	0	0	0
	ADVM-022 Related**	6	33	5	25	5	19	9	55
	Total Ocular	6	58	6	44	9	49	9	71
Non-Ocular†	Serious	1	1	2	7	2	3	0	0
	Total Non-Ocular†	5	21	6	18	6	13	4	5

**Retinal detachment (unrelated to ADVM-022) and recurrent moderate uveitis (likely related to ADVM-022)*
*** ADVM-022 related ocular events were mild (83%) or moderate (17%)*
†None of the non-ocular AEs were ADVM-022 related

Data cut: July 16, 2021

Safety Summary – IOP

- No cases of clinically-relevant decrease in IOP observed in all patients in both 2×10^{11} and 6×10^{11} doses



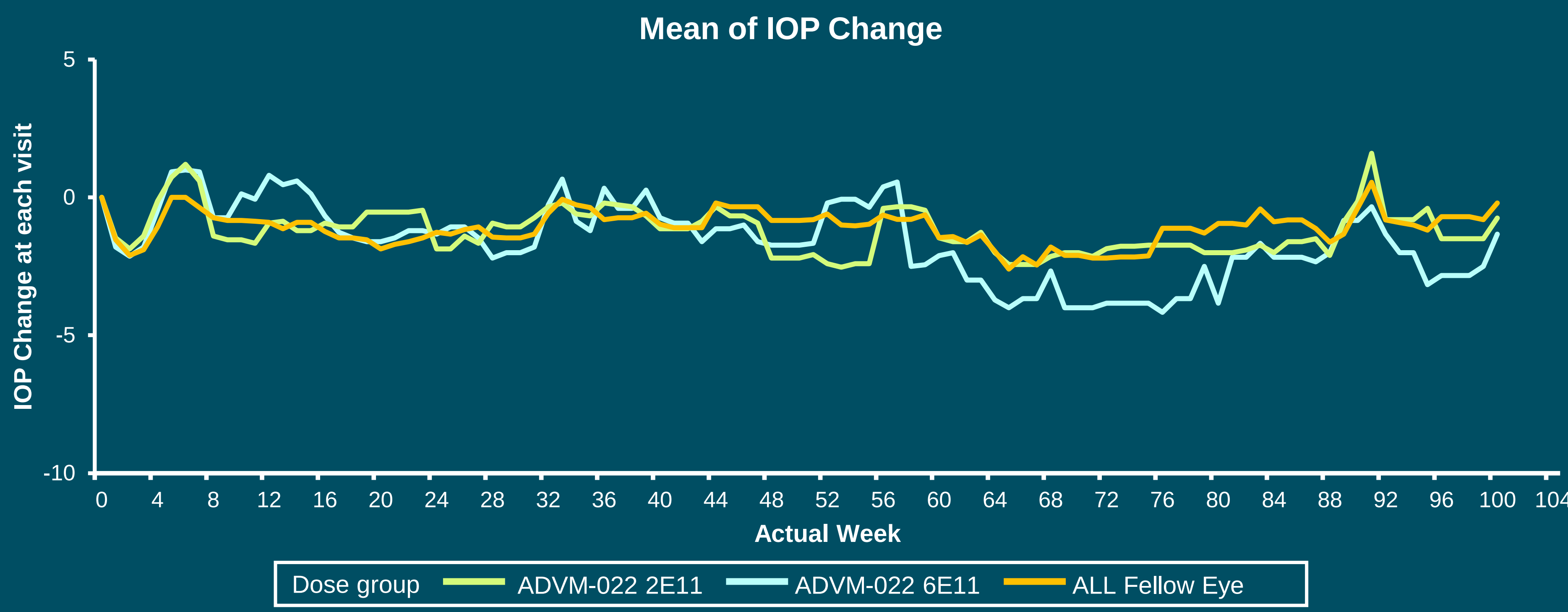
ADVM-022 2E11	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	14	14	13	11	11	11	11	11	10	10	7	5	5	4	4	4
ADVM-022 6E11	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	13	8	9	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

IOP, intraocular pressure.

Data cut: July 16, 2021

Safety Summary – IOP

- No cases of clinically-relevant decrease in IOP observed in all patients in both $2{\times}10^{11}$ and $6{\times}10^{11}$ doses

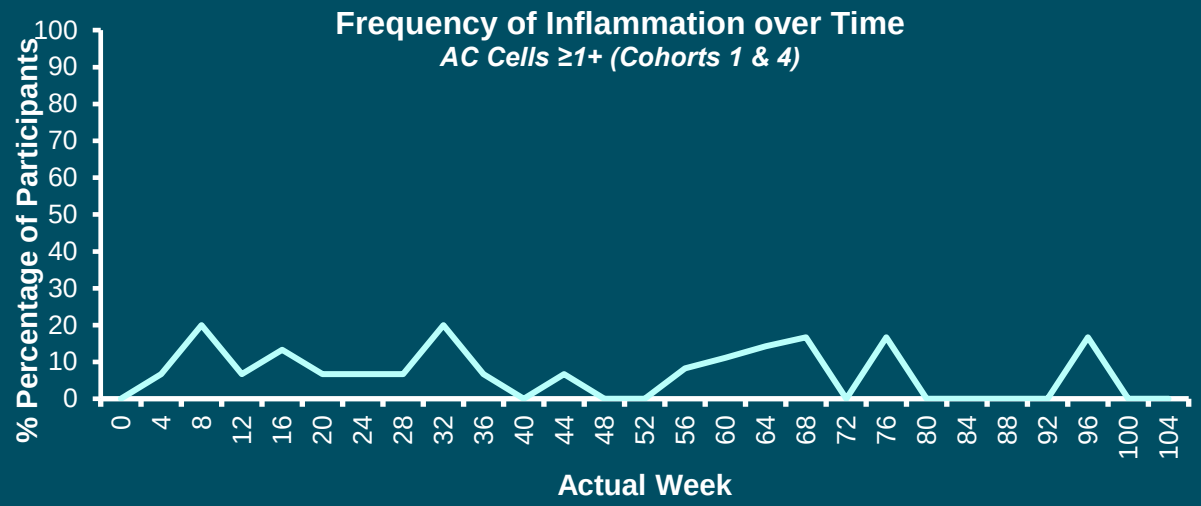


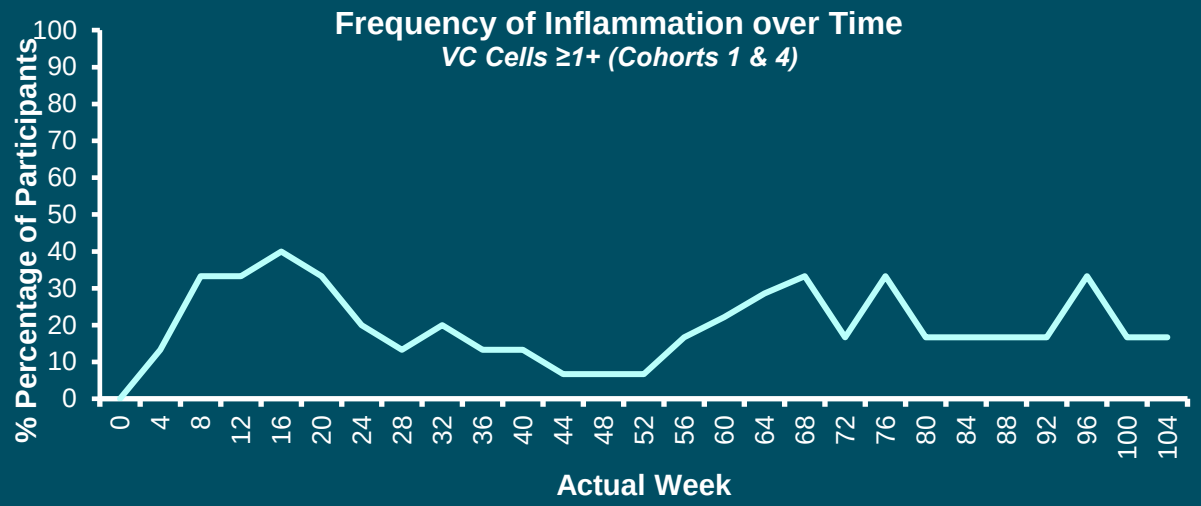
ADVM-022 2E11	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	14	14	13	11	11	11	11	11	10	10	7	5	5	4	4	4
ADVM-022 6E11	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	13	8	9	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
ALL Fellow Eye	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	28	24	24	22	22	20	20	20	20	19	17	17	17	17	17	16	16	13	11	11	10	10	10

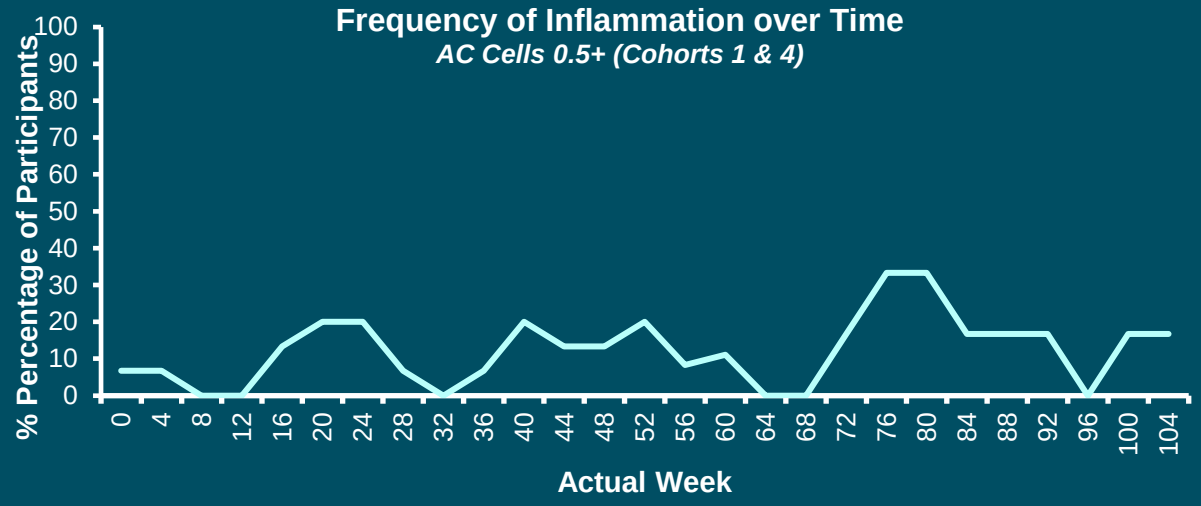
IOP, intraocular pressure.

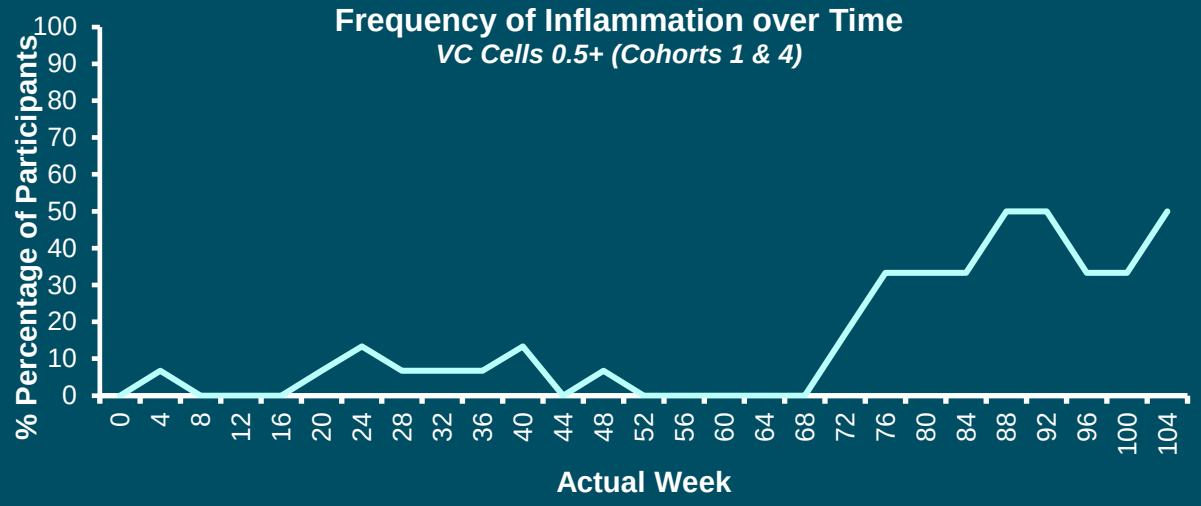
Data cut: July 16, 2021

Immune Response Observed with 6×10^{11} vg/eye dose









N	15	15	15	15	15	15	15	15	15	15	15	15	15	15	12	9	7	6	6	6	6	6	6	6	6	6

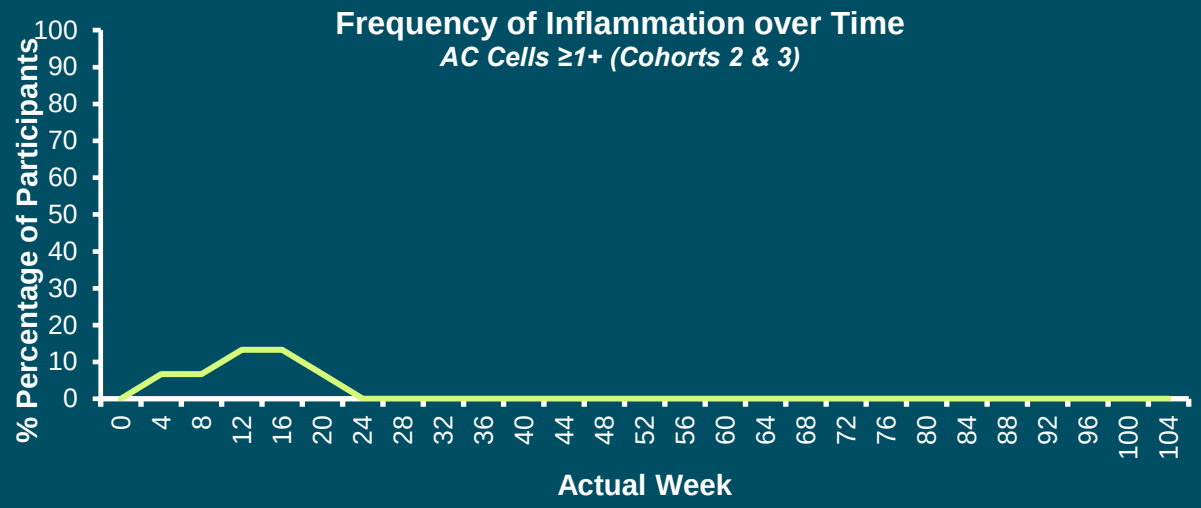
N	15	15	15	15	15	15	15	15	15	15	15	15	15	15	12	9	7	6	6	6	6	6	6	6	6	6

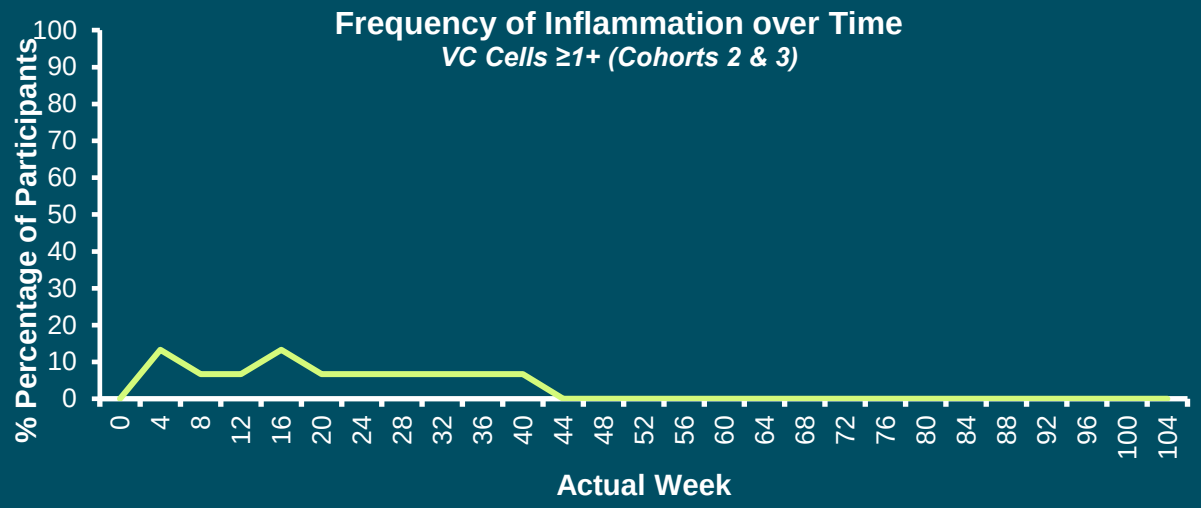
Cell grades as assessed by slit lamp
Grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria for aqueous cells and National Institutes of Health (NIH) guidelines for vitreous cells.
Aqueous cells (AC): 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >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

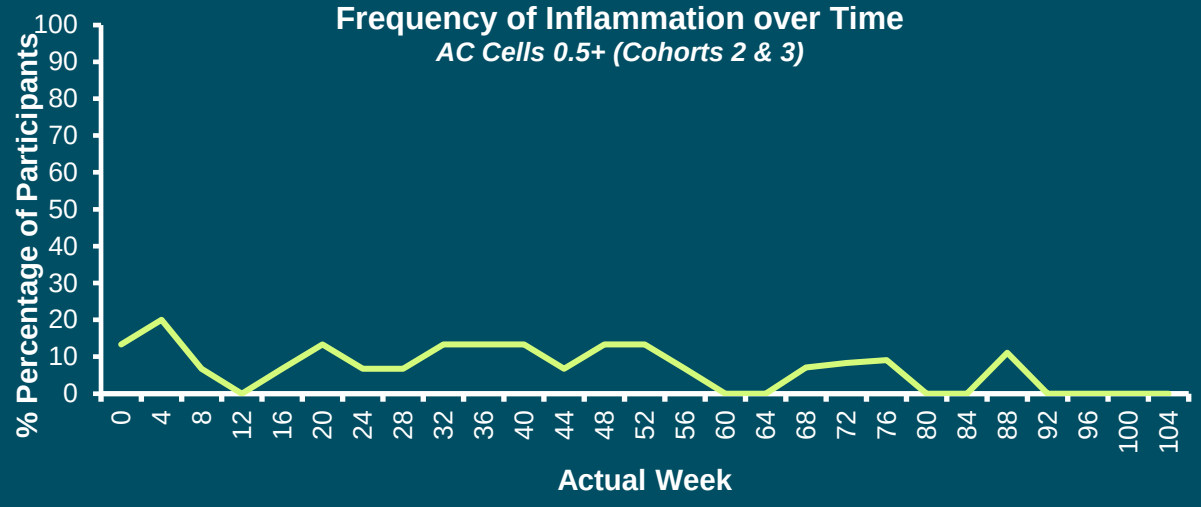
Data cut: July 16, 2021

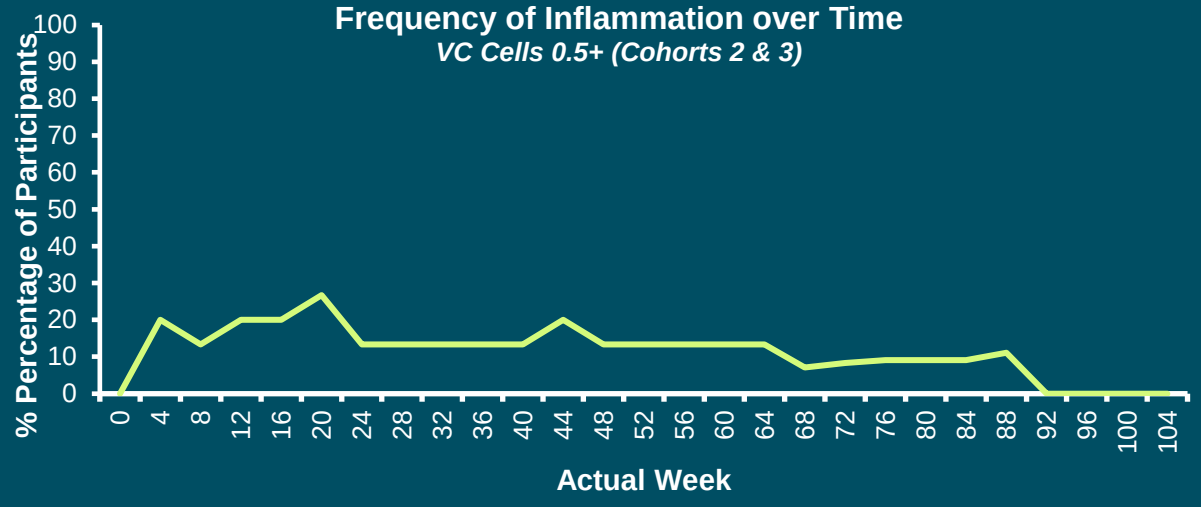
Lower Immune Response Observed with 2×10^{11} vg/eye dose

Frequency of inflammation decreases over time









N	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	12	11	11	11	9	5	4	4	4

N	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	12	11	11	11	9	5	4	4	4

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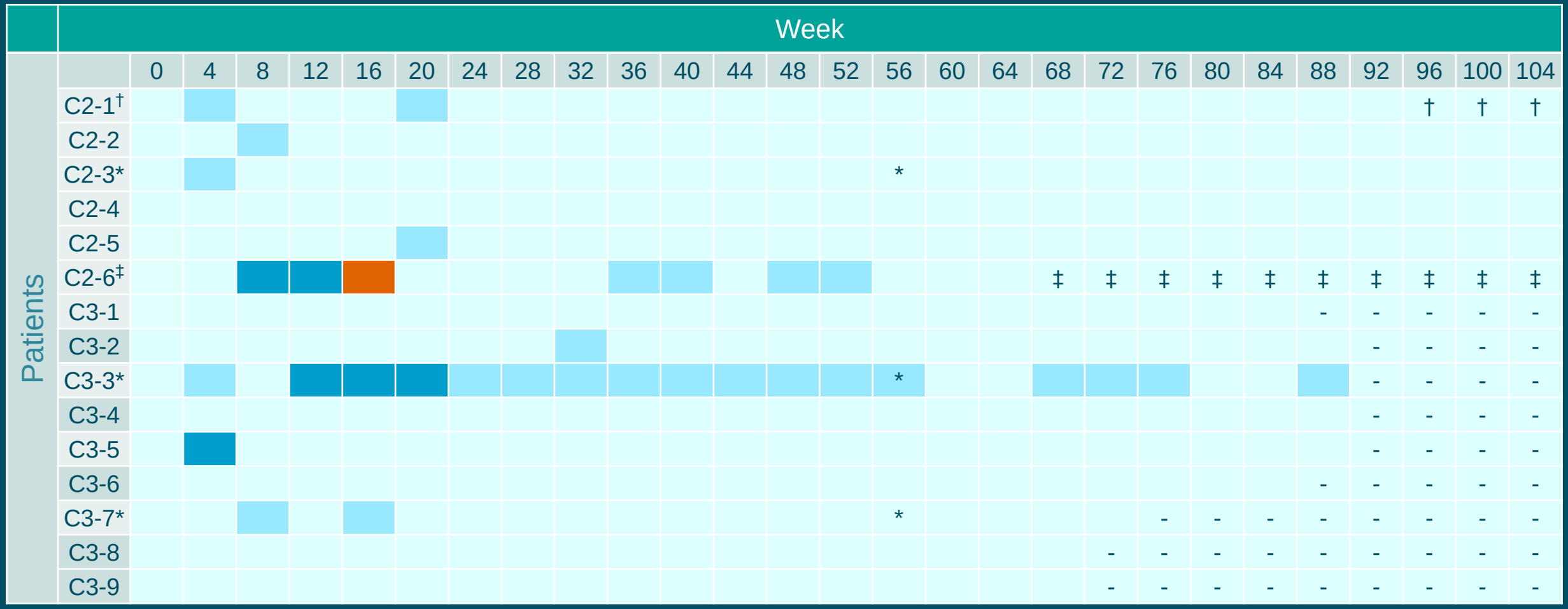
Data cut: July 16, 2021

AC – Inflammation was Mild and Decreasing Over Time in Cohorts 2 and 3 *[2×10^{11} vg/eye dose]*



**Cataract surgery before Week 56*

†A patient died of a cardiopulmonary arrest due to hypoxia ~96 weeks; ‡A patient missed visits after Week 64 due to worsening of COPD and died of lung malignancy at ~76 weeks

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.

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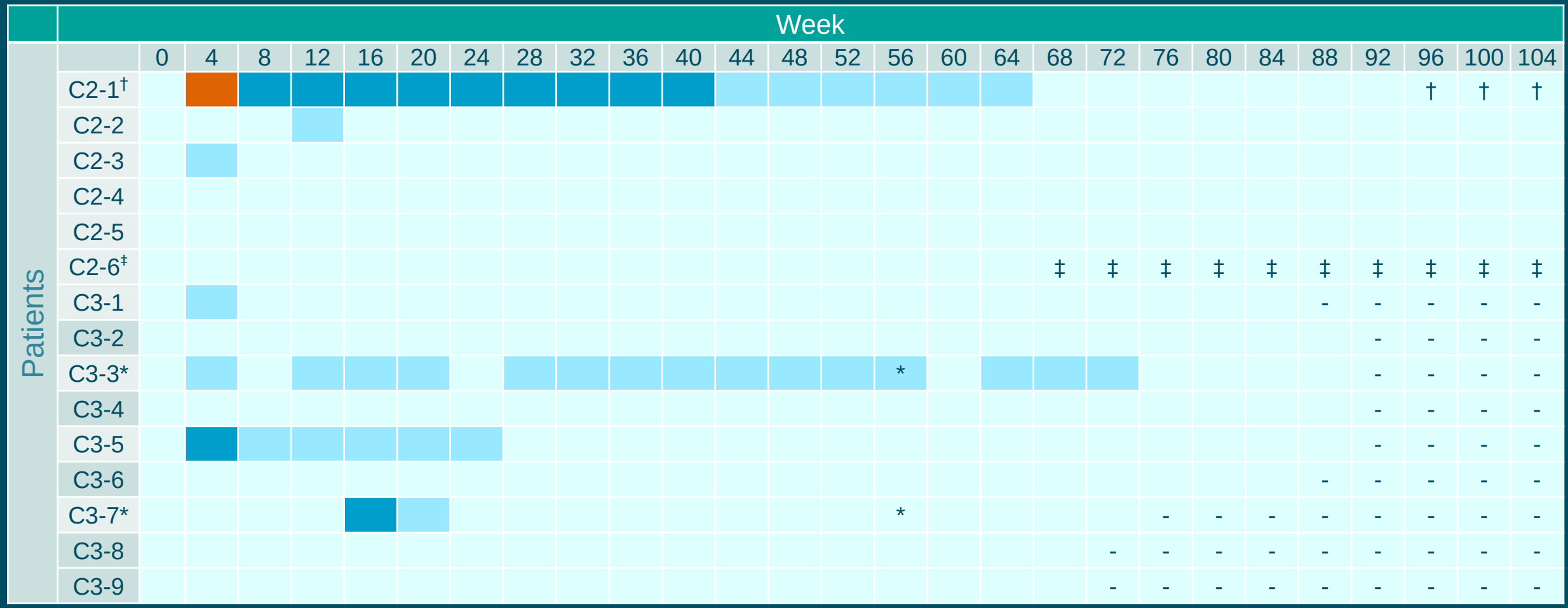
Data cut: July 16, 2021

VC – Inflammation was Mild and Decreasing Over Time in Cohorts 2 and 3 *[2×10^{11} vg/eye dose]*



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Data cut: July 16, 2021

Steroid Eye Drops Post Prophylaxis Decrease Over Time in Cohorts 2 and 3

13-day oral prophylaxis

Patients	Week 0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104
C2-1†		4	4	4	4	4	4	4	4	2	2	1	1	1	1	1	1								†	†	†
C2-2				1	2																						
C2-3		3																									
C2-4																											
C2-5																											
C2-6‡			2	2	4	4	2	1	0.5	1	2	2	2	3	3	3	3	‡	‡	‡	‡	‡	‡	‡	‡	‡	‡
C3-1	4	2																			-	-	-	-	-	-	-
C3-2	4	2							3	3	3	3									-	-	-	-	-	-	-
C3-3*	4	3	2	3	2	3	4	4	4	4	4	4	4	4	4*	3	3	2	1	1	-	-	-	-	-	-	-
C3-4	4	2					2	2	2												-	-	-	-	-	-	-
C3-5	4	4	2	1																	-	-	-	-	-	-	-
C3-6	4	2																			-	-	-	-	-	-	-
C3-7*	4	2	2	2	3	4	4	3	2	1	1	0.5	0.5	0.5	1*	1	1	1	1	-	-	-	-	-	-	-	-
C3-8	4	2																	-	-	-	-	-	-	-	-	-
C3-9	4	2																	-	-	-	-	-	-	-	-	-

6-week prophylaxis steroid eye drops

# of daily drops: 0 | 0.5 | 1 | 2 | 3 | 4 | - No assessment

*Cataract surgery before Week 56

†A patient died of a cardiopulmonary arrest due to hypoxia ~96 weeks; ‡A patient missed visits after Week 64 due to worsening of COPD and died of lung malignancy at ~76 weeks

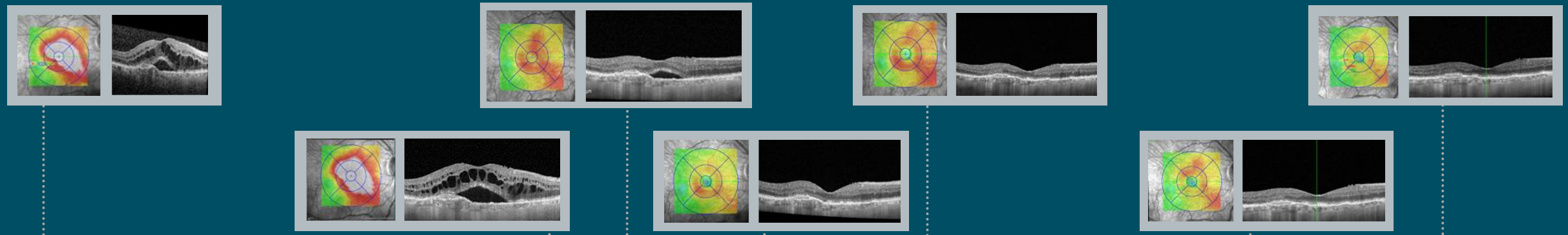
0.5 represents drops every other day

Data cut: July 16, 2021

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

OPTIC Gene Therapy in nAMD

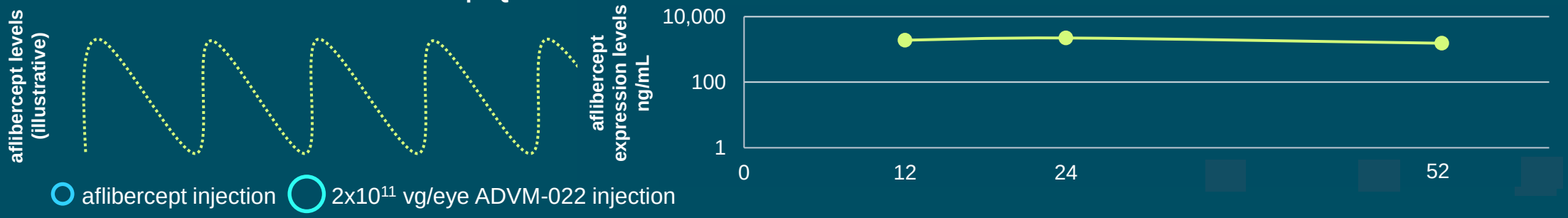
Patient Case from Cohort 3 [2E11]: 82-year-old male with 19 IVTs prior to study with 9 IVTs in the last 12 months



Persistent fluid despite frequent anti-VEGF injections

-30 wks	-2 wks	Day 0	+12 wks	+24 wks	+52 wks	+68 wks
	BCVA: 75 letters CST: 664 µm	ADVM-022	BCVA: 81 letters CST: 257 µm	BCVA: 83 letters CST: 272 µm	BCVA: 83 letters CST: 281 µm	BCVA: 84 letters CST: 281 µm

Treatment with aflibercept Q5W



Data cut: July 16, 2021

2-year Outcomes from OPTIC with a Single-IVT Injection of ADVM-022 in Neovascular AMD

- **ADVM-022 provides robust aflibercept expression and sustained efficacy with both doses in a heavily treatment-experienced patient population beyond 2-years**
  - Patients maintained vision (BCVA), stable to improved retinal anatomy (CST)
  - Aflibercept protein expression within targeted therapeutic range and stable out to 104 weeks
- **>80% reduction in annualized injection frequency at 2×10^{11} vg/eye dose**
- **Low 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
- **No clinically relevant low IOP events observed at either dose**
- **Cohort 2 & 3 provide continued evidence of efficacy, safety, and durability at 2×10^{11} vg/eye through a median follow-up of 1.7 years with limited prophylaxis**
  - 5-years planned follow-up
- **Further studies are warranted at 2×10^{11} vg/eye and lower doses and investigating enhanced prophylaxis**

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

Data cut: July 16, 2021

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