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

Dante Pieramici, MD

- On behalf of the OPTIC Investigators -

ASRS 2021 | San Antonio, TX | October 8 – October 12, 2021

Disclosures

- *Consultant/Advisory*: Genentech, Regeneron, RegenX Bio, Adverum, Gemini, NGM, IVERIC,

- *Research Funding:* Genentech, Regeneron, RegenX Bio, Adverum, Gemini, NGM, Stealth, Unity, Apellis, Novartis, Kodiac, Chengdu Kanghong, IVERIC, Ocular Therapeutix

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

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*

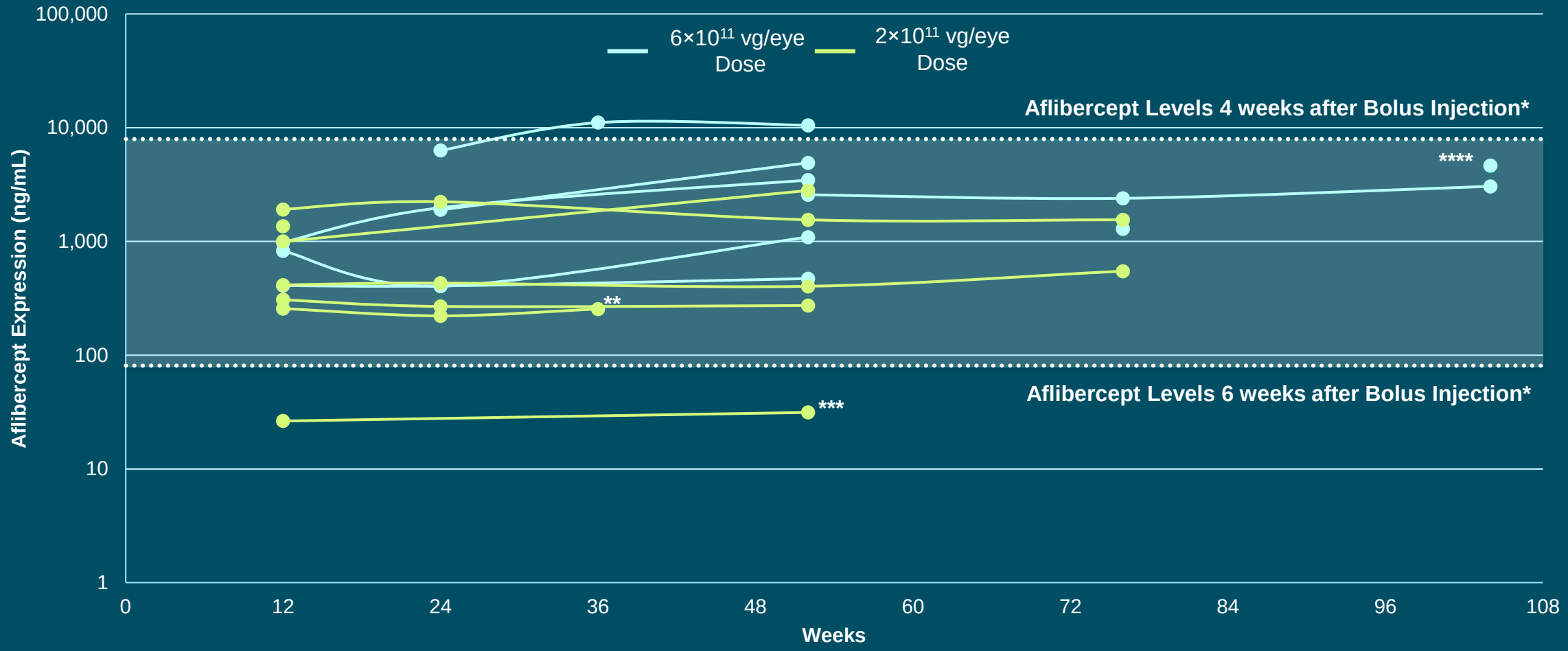
Neovascular AMD Study Population Previously Required Frequent Injections to Maintain Vision

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

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

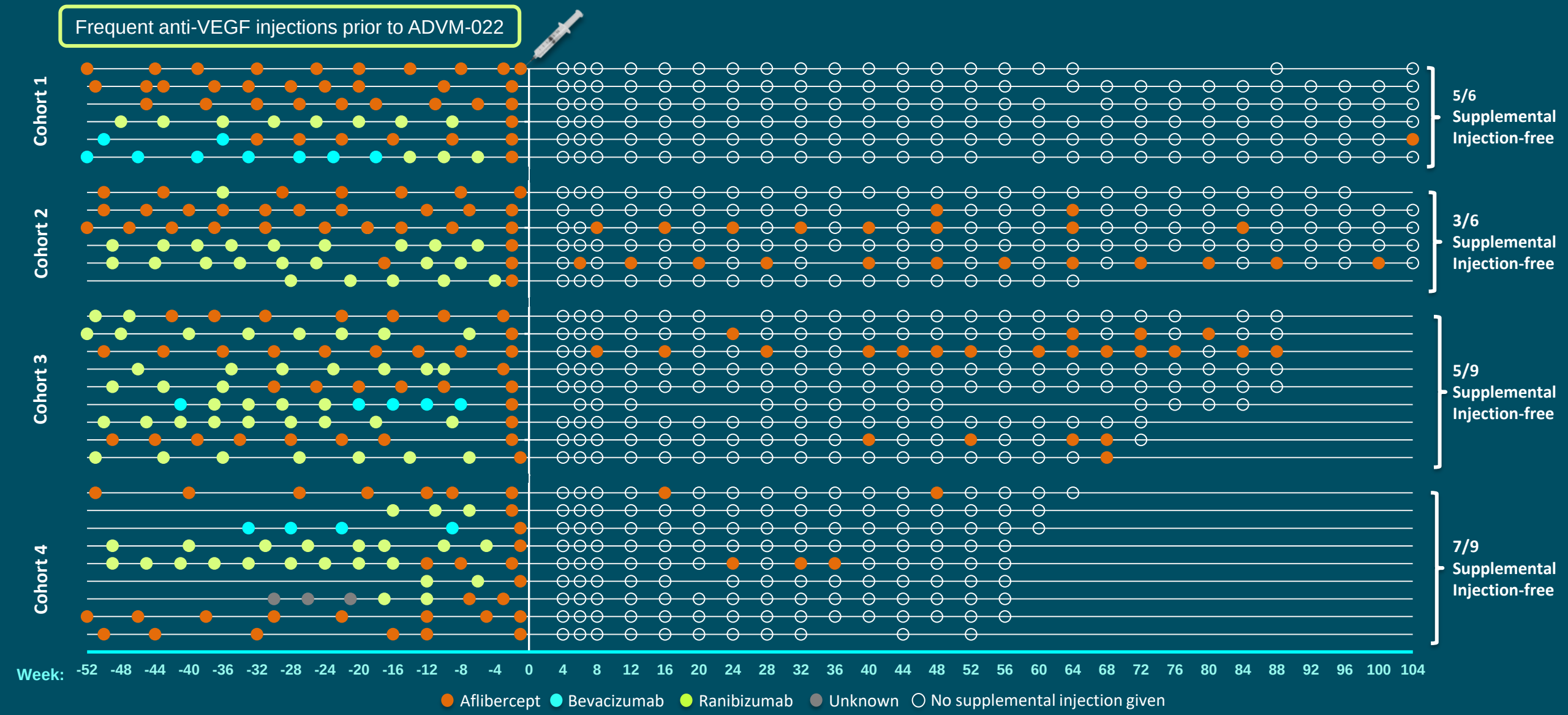
Within modeled aflibercept pharmacokinetic range post single Aflibercept 2mg at 4- and 6-weeks dosing



**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.

Data cut: July 16, 2021

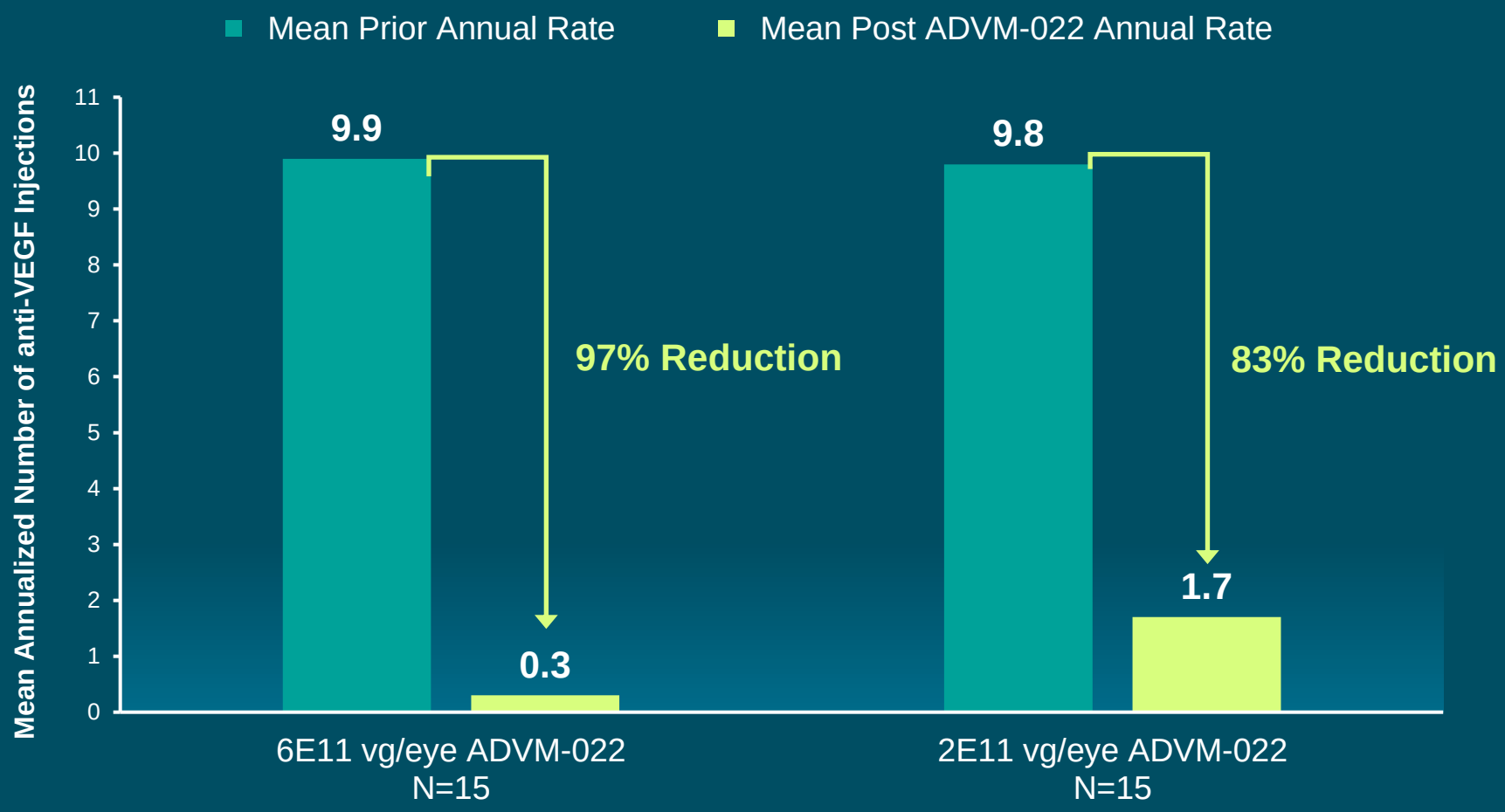
Majority of Patients are Supplemental Injection Free after a Single IVT Injection of ADVM-022 in OPTIC



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.*

Data cut: July 16, 2021

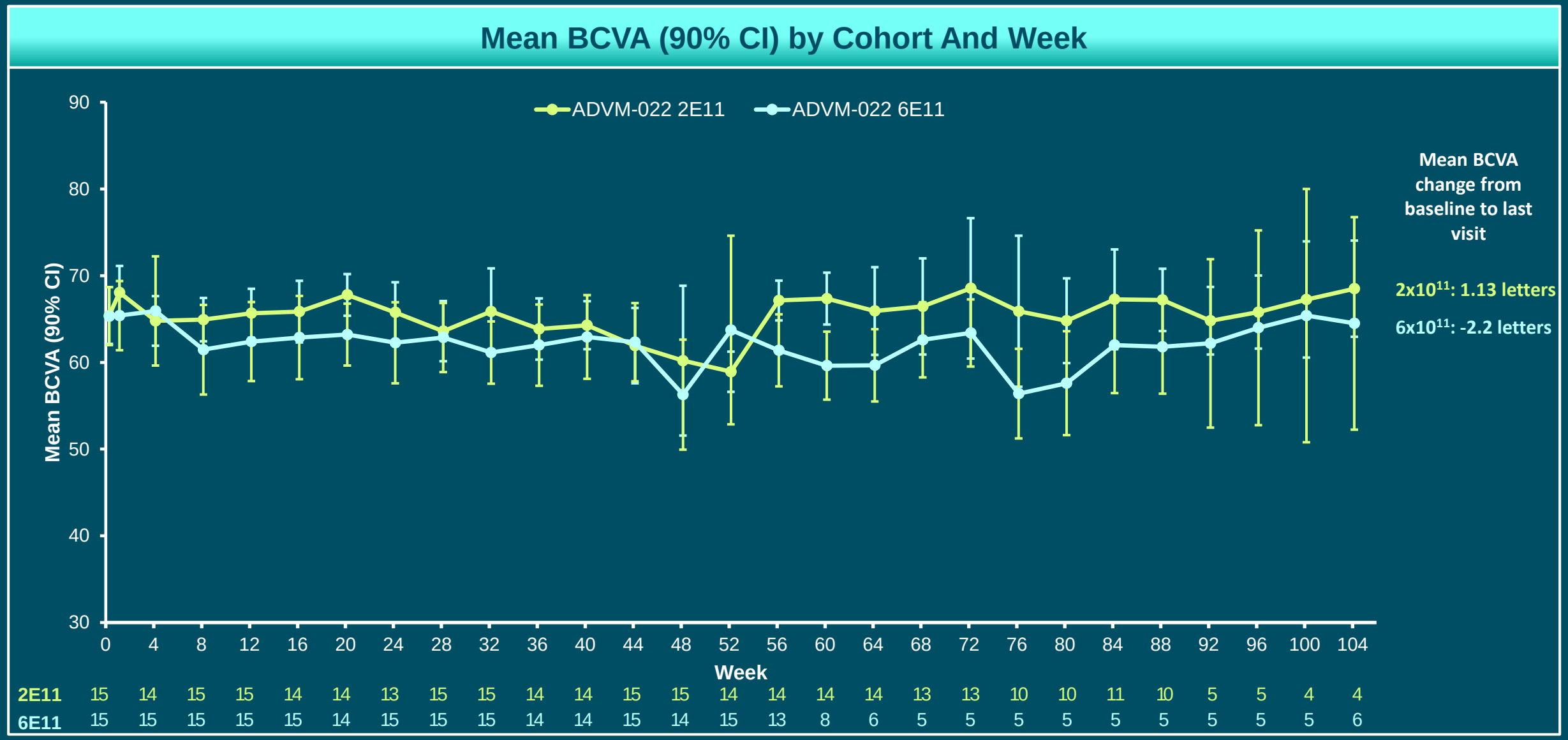
>80% Reduction in Annualized Anti-VEGF Injections Observed Following $2x10^{11}$ ADVM-022 IVT Injection



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).

Data Cut: July 16, 2021

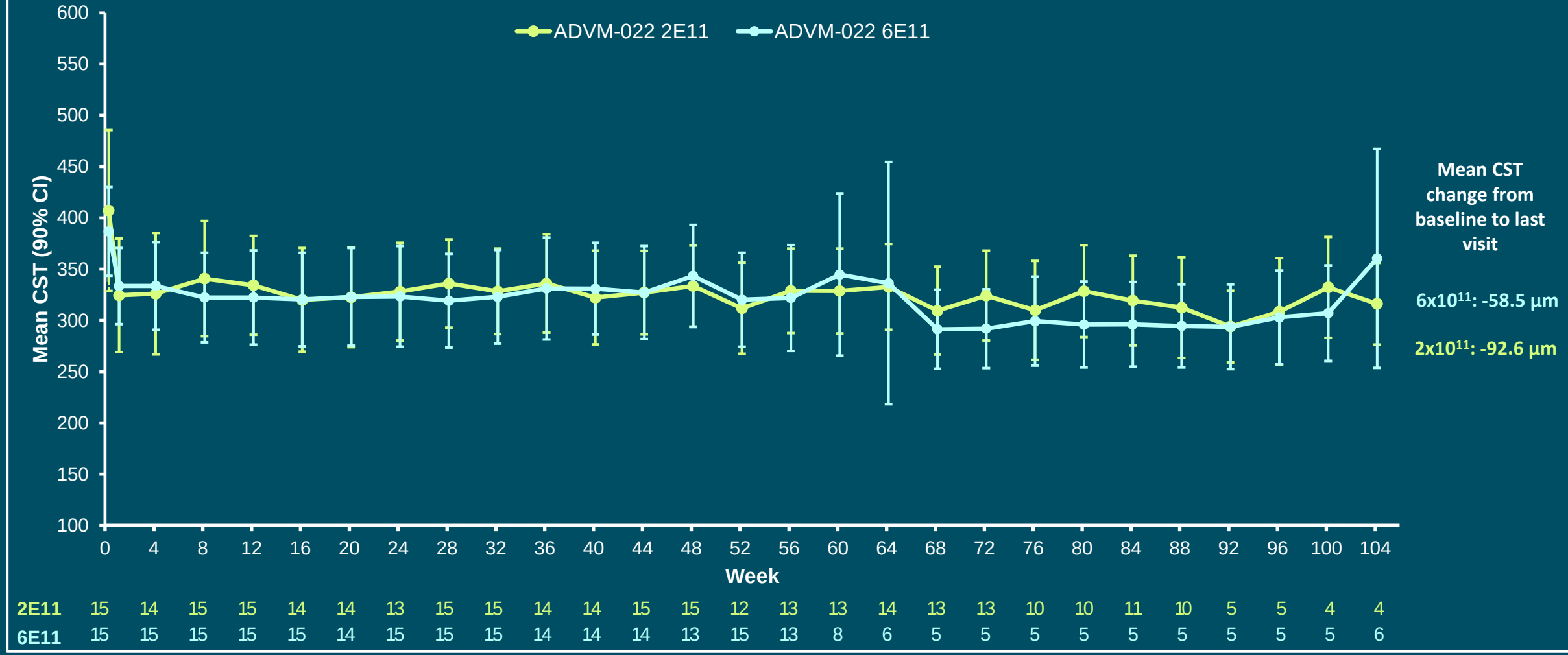
BCVA Maintained Over Time Across Both Dose Groups



Data cut: July 16, 2021

CST Maintained Over Time Across Both Dose Groups

Mean CST (90% CI) by Cohort And Week



Data cut: July 16, 2021

Safety Summary Across Cohorts

- No ADVM-022-related non-ocular adverse events†
- 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%)‡

†2 patients (Cohort 2) died in the study;1 patient died of lung malignancy ~76 weeks and 1 patient died of a cardiopulmonary arret due to hypoxia ~96 weeks.

**Fluorescein angiography of posterior pole.*

‡One AE of moderate recurrent uveitis deemed to be related to ADVM-022 was responsive to steroid eye drops (Cohort 1).

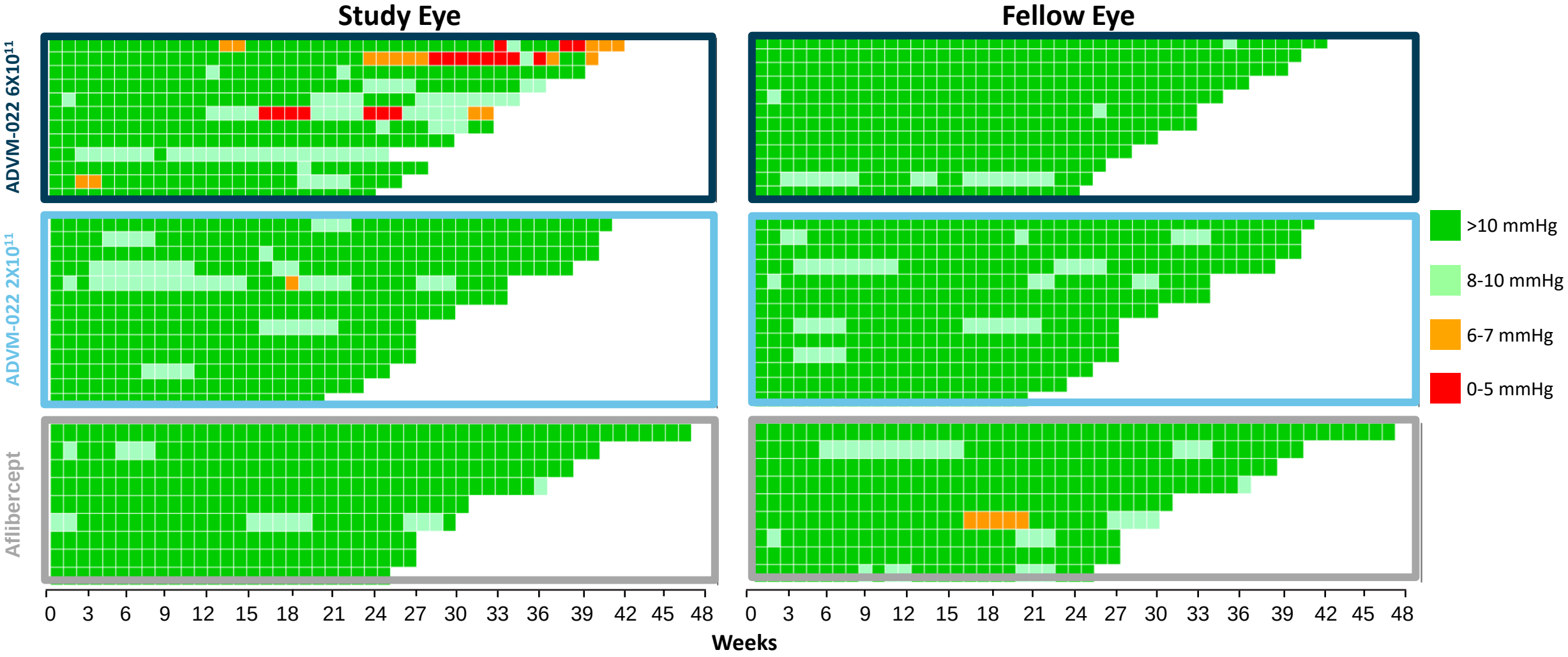
One unrelated ocular SAE of retinal detachment surgically repaired and resolved (Cohort 1)

IOP, intraocular pressure; AEs, adverse events; SAEs, serious AEs

Data cut: July 16, 2021

INFINITY Study: Unexpected AE of Hypotony at ADVM-022 6x10^{11} Dose in DME

Dose-Dependent Changes in IOP Over Time



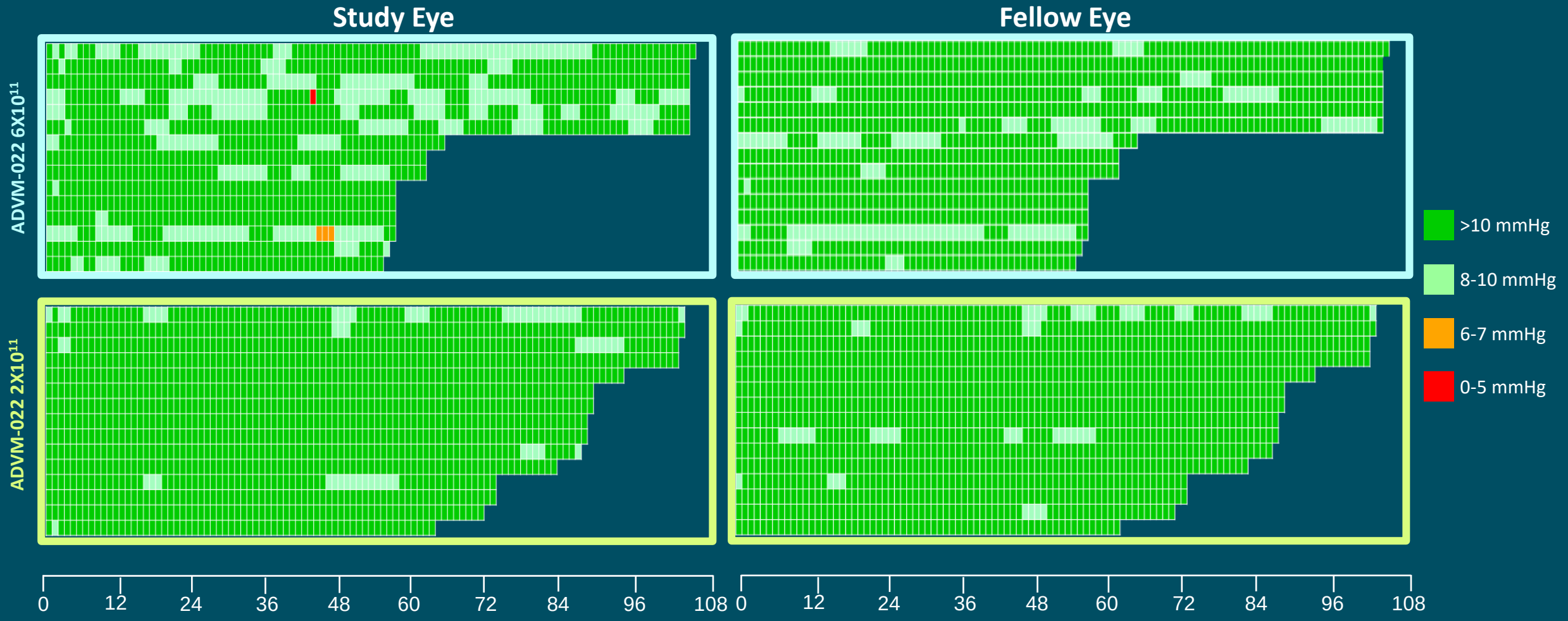
Three patients in the ADVM-022 6x10^{11} arm underwent surgery at week 35 (n=1) and 37 (n=2)

AE, adverse event; DME, diabetic macular edema; IOP, intraocular pressure

Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

Data cut off: June 22, 2021; All data unmasked: May 4, 2021

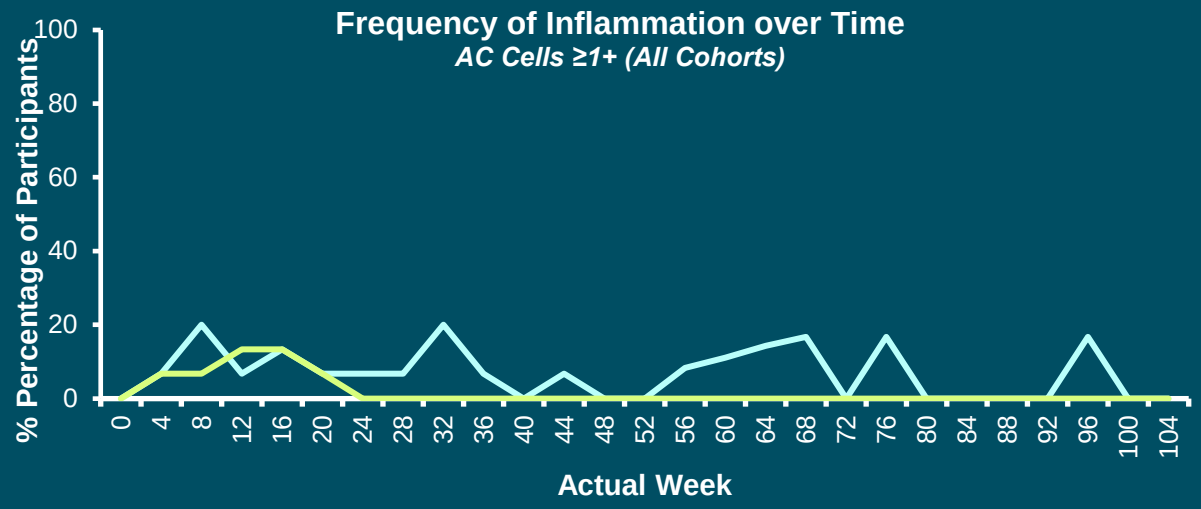
OPTIC Study: IOP Over Time in Patients with nAMD

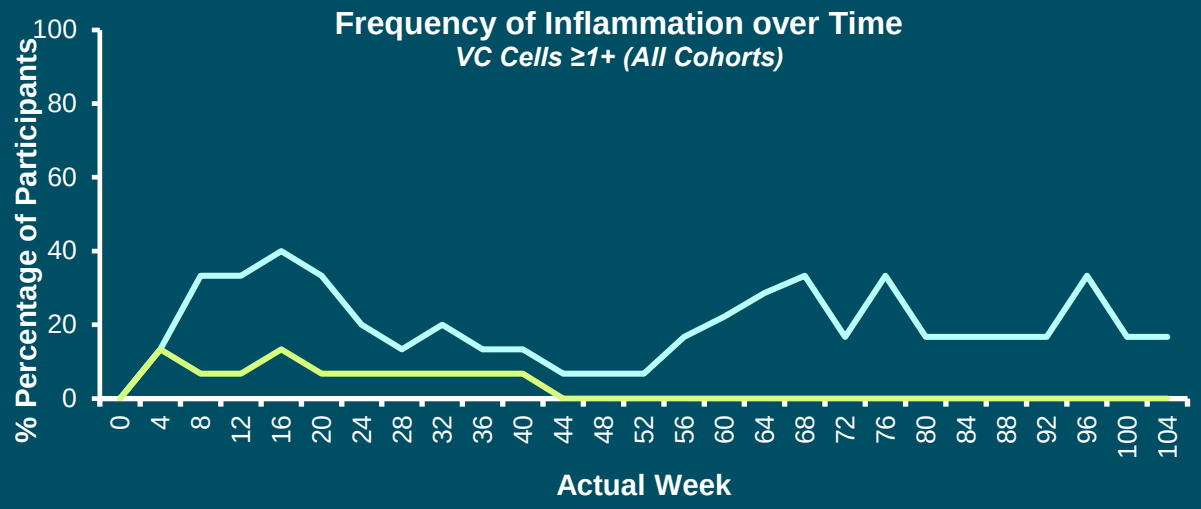


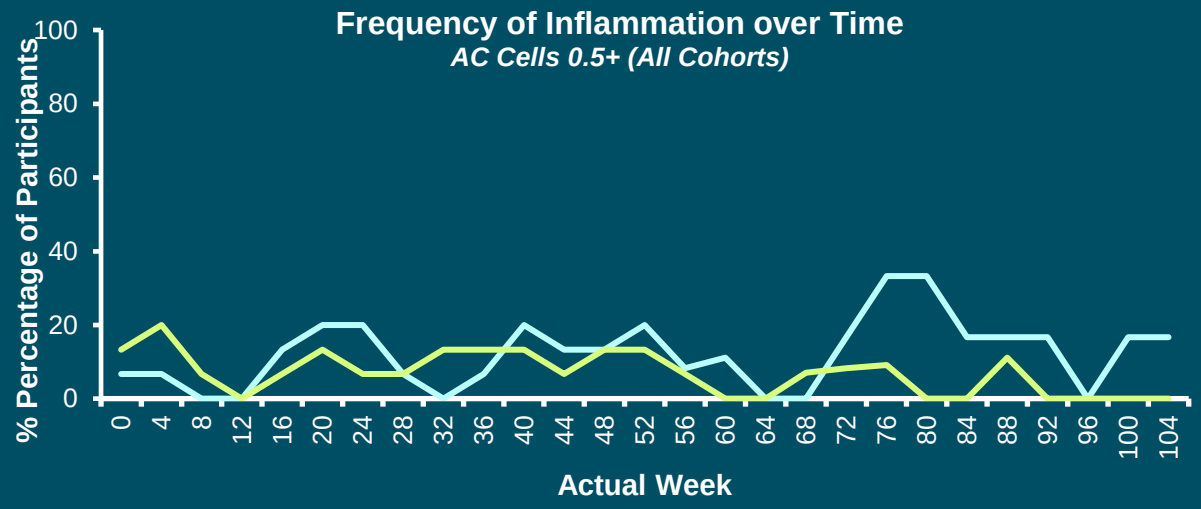
Data cut: July 16, 2021

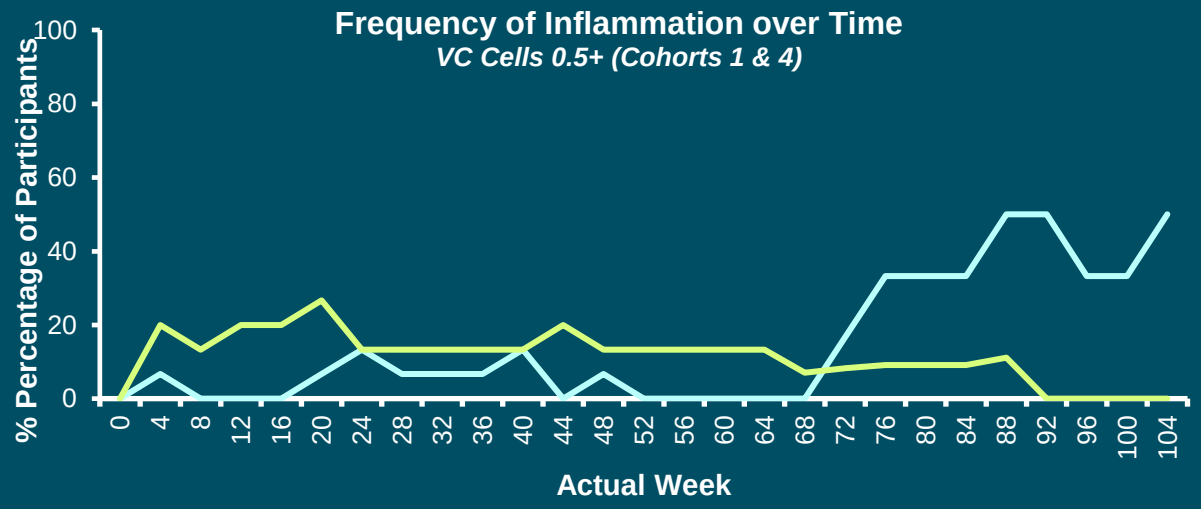
Lower Immune Response Observed with 2×10^{11} vg/eye dose

Frequency of inflammation decreases over time









		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
2E11	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
6E11	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	6

		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
	N	15	15	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	12	9	7	6	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.

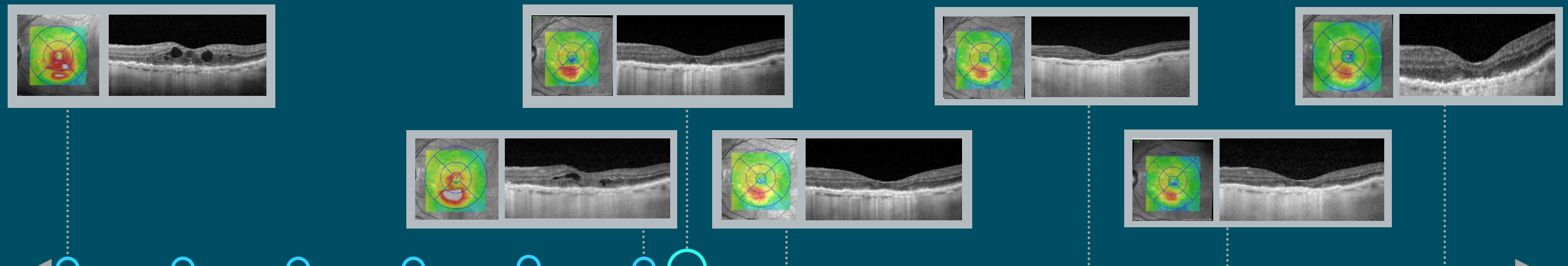
Aqueous cells (AC): 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells

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

Case Study: A Single IVT Injection of ADVM-022 $2x10^{11}$ vg/eye eliminates fluctuations in fluid and CST

Patient Case from Cohort 3 [2E11]: 90-year-old female with 21 IVTs prior to study with 9 IVTs in the last 12 months



-56 wks

-2 wks
BCVA: 53 letters
CST: 358µm

Day 0
ADVM-022

+12 wks
BCVA: 66 letters
CST: 237µm

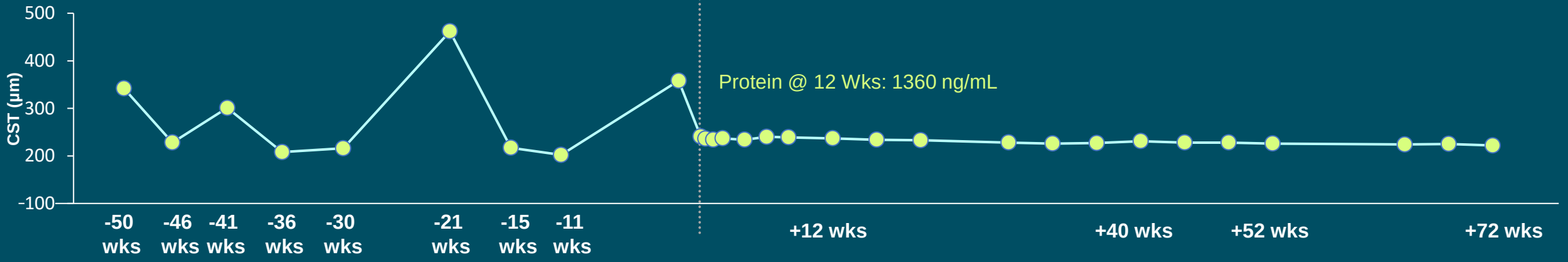
+40 wks
BCVA: 71 letters
CST: 231 µm

+52 wks
BCVA: 69 letters
CST: 226 µm

+72 wks
BCVA: 72 letters
CST: 222 µm

Treatment with aflibercept Q5W

aflibercept injection | $2x10^{11}$ vg/eye ADVM-022 injection



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**
- **>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**
- **No clinically relevant low IOP events observed at either dose in nAMD patients**
- **Further studies of ADVM-022 in nAMD are warranted, and could include evaluation of 2×10^{11} vg/eye and lower doses with enhanced prophylaxis regimens**

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

ADVM-022 Acknowledgments

Investigators, Study Teams and Patients

- 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
- Julie Clark, MD
- Carol Hoang PharmD
- Adam Turpcu PhD

Thank you