Intravitreal Gene Therapy for Diabetic Macular Edema with ADVM-022: Prospective, Randomized Phase 2 INFINITY Trial

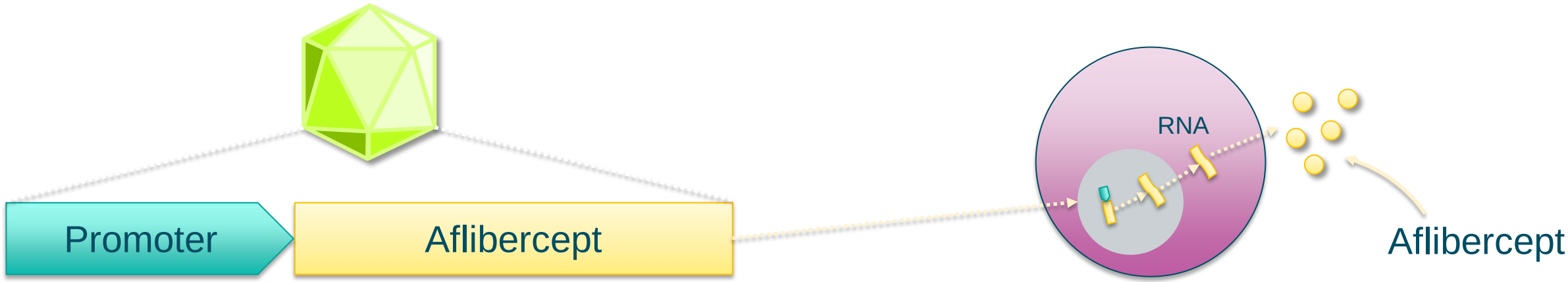
David Boyer, MD

on behalf of the INFINITY investigators

ADVM-022 is a Novel Biofactory Approach to Gene Therapy

Designed for continuous delivery of aflibercept by intravitreal injection

AAV.7m8 capsid[a]



Aflibercept Expression Cassette

Target Retinal Cell Expresses Aflibercept

Strong, Ubiquitous Promoter Designed for Robust Protein Expression

Codon-Optimized cDNA

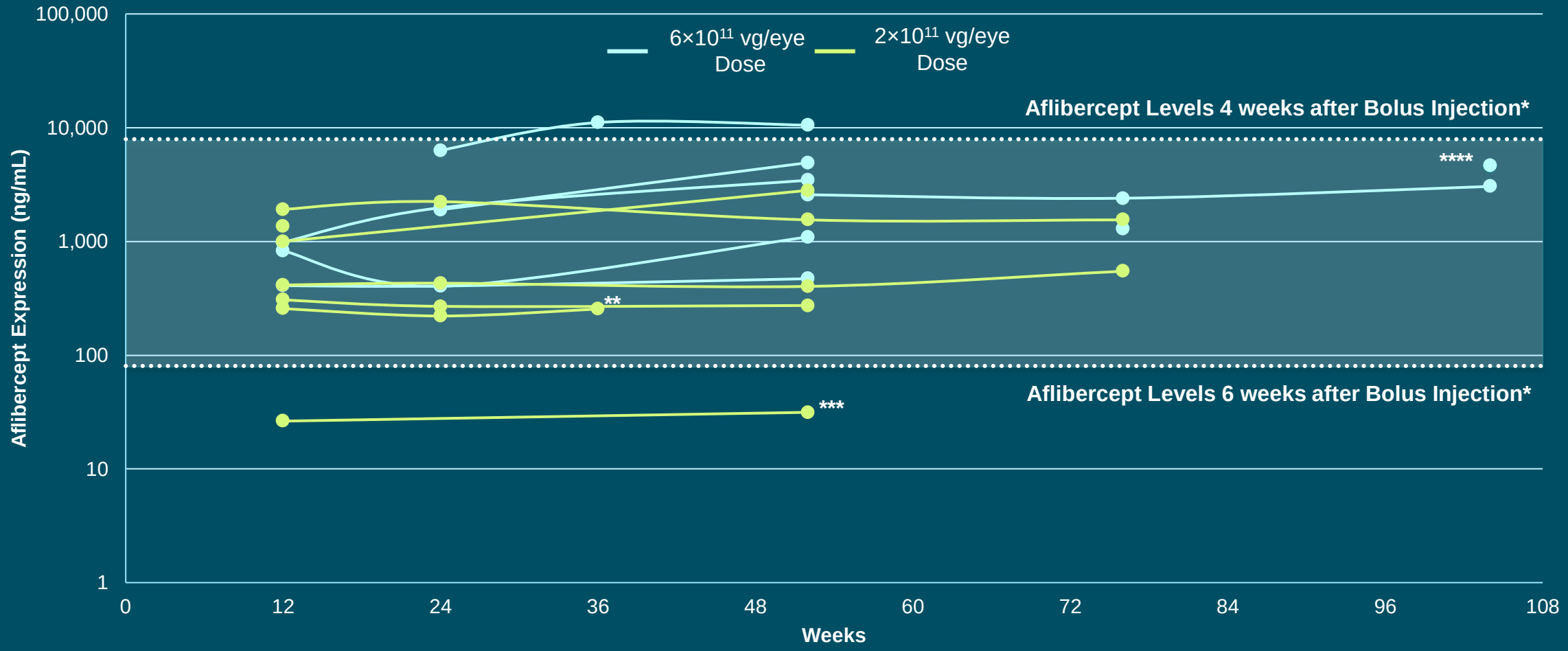
[a]*Capsid Engineered from Wild-Type AAV2 by Directed Evolution and Screened for Highly Efficient Retinal Transduction Following IVT Injection*

IVT, intravitreal

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

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

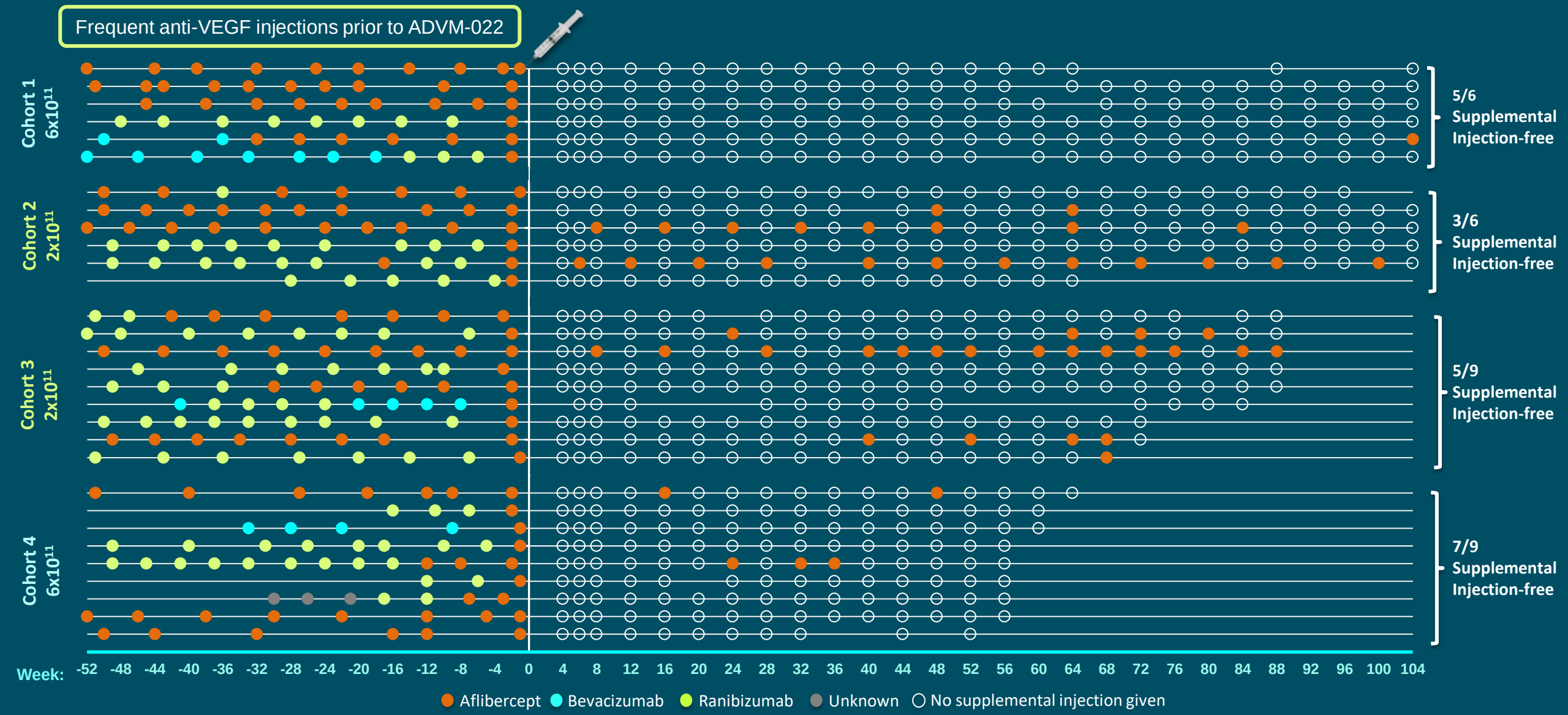
ADVM-022 Intravitreal Gene Therapy: Experience from OPTIC Study

Neovascular AMD Study Population Previously Required Frequent Injections to Maintain Vision

Baseline Characteristics	Cohort 1 $6x10^{11}$ vg/eye (N=6)	Cohort 2 $2x10^{11}$ vg/eye (N=6)	Cohort 3 $2x10^{11}$ vg/eye (N=9)	Cohort 4 $6x10^{11}$ vg/eye (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

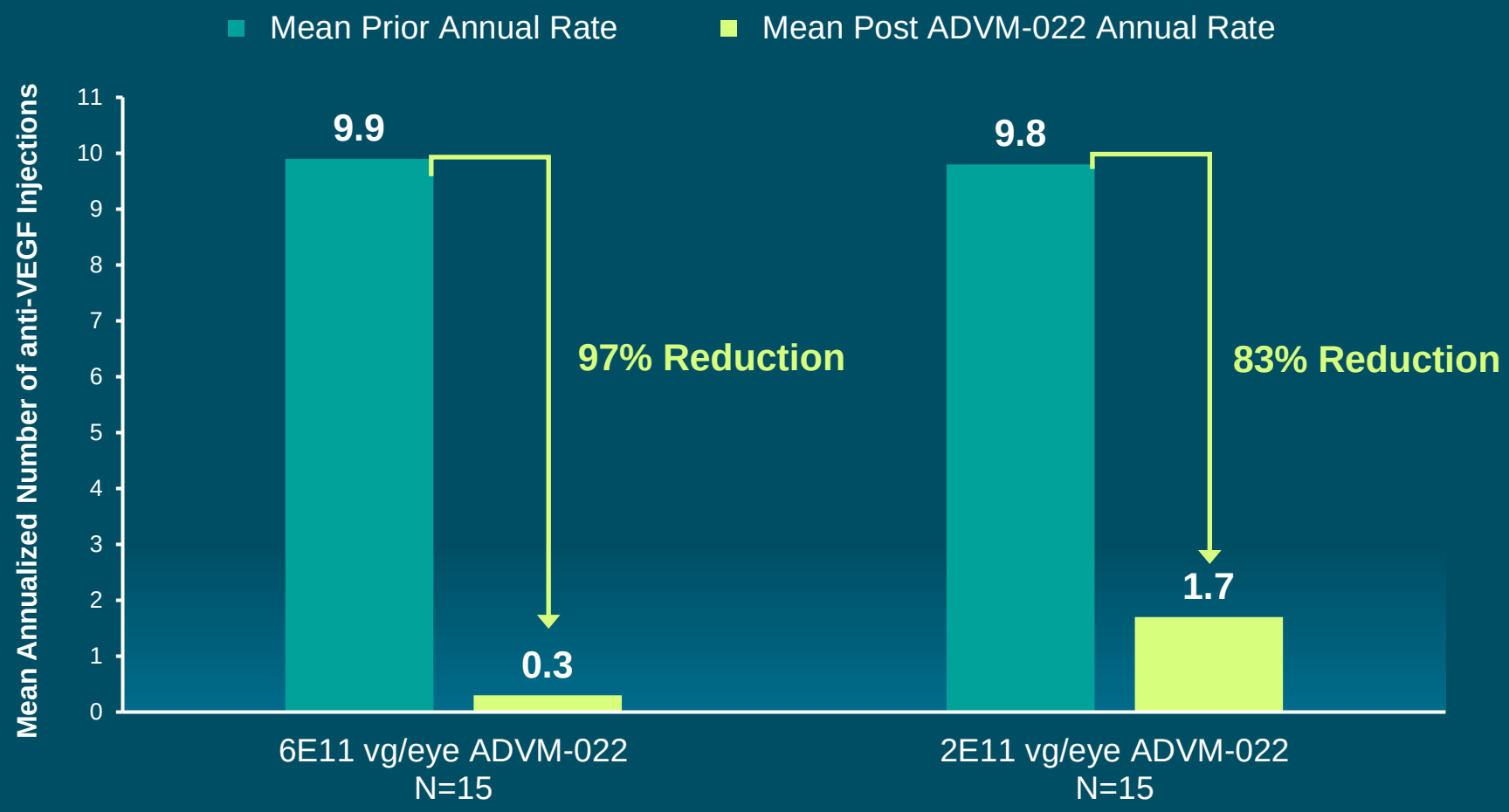
Majority of Patients are Supplemental Injection Free after a Single IVT Injection of ADVM-022 in OPTIC



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

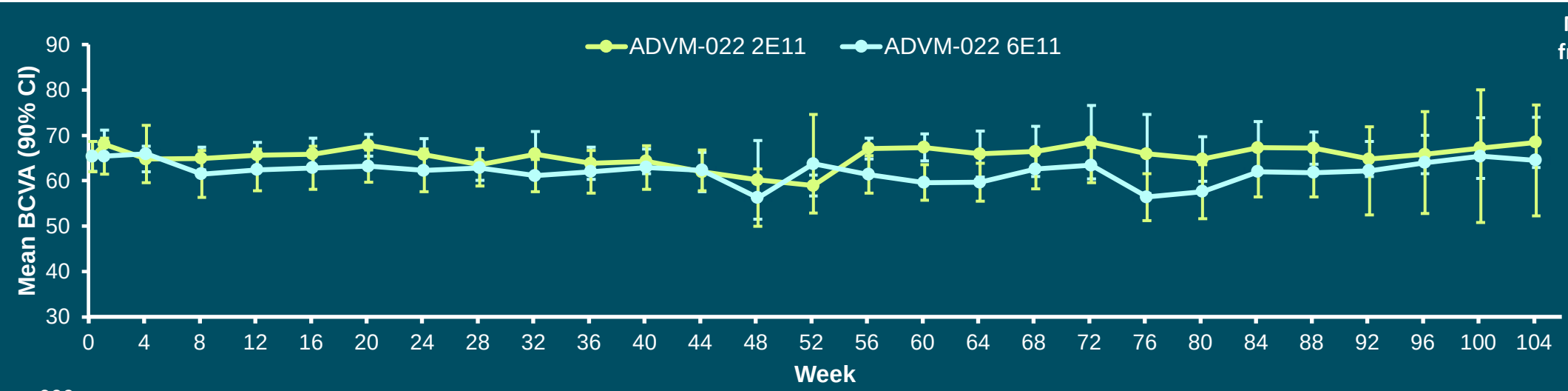


Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).

Data Cut: July 16, 2021

BCVA and CST Maintained Over Time Across Both Dose Groups

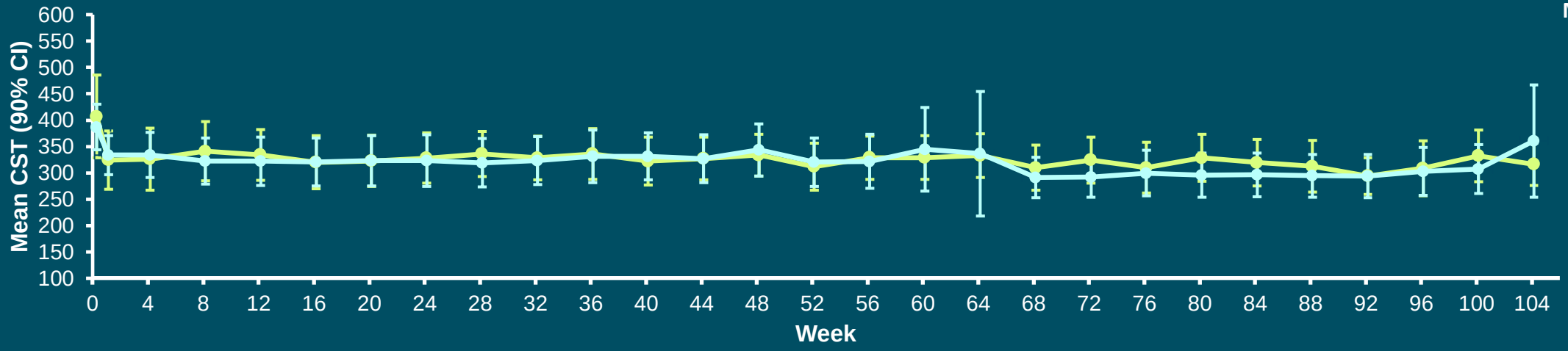
Mean BCVA (90% CI) and Mean CST (90% CI) by Dose and Week



Mean BCVA change from baseline to last visit

$2x10^{11}$: 1.13 letters

$6x10^{11}$: -2.2 letters



Mean CST change from baseline to last visit

$6x10^{11}$: -58.5 µm

$2x10^{11}$: -92.6 µm

2E11	15	14	15	15	14	14	13	15	15	14	14	15	15	14	14	14	14	13	13	10	10	11	10	5	5	4	4	
6E11	15	15	15	15	15	14	15	15	15	14	14	15	14	15	13	8	6	5	5	5	5	5	5	5	5	5	6	

Data cut: July 16, 2021

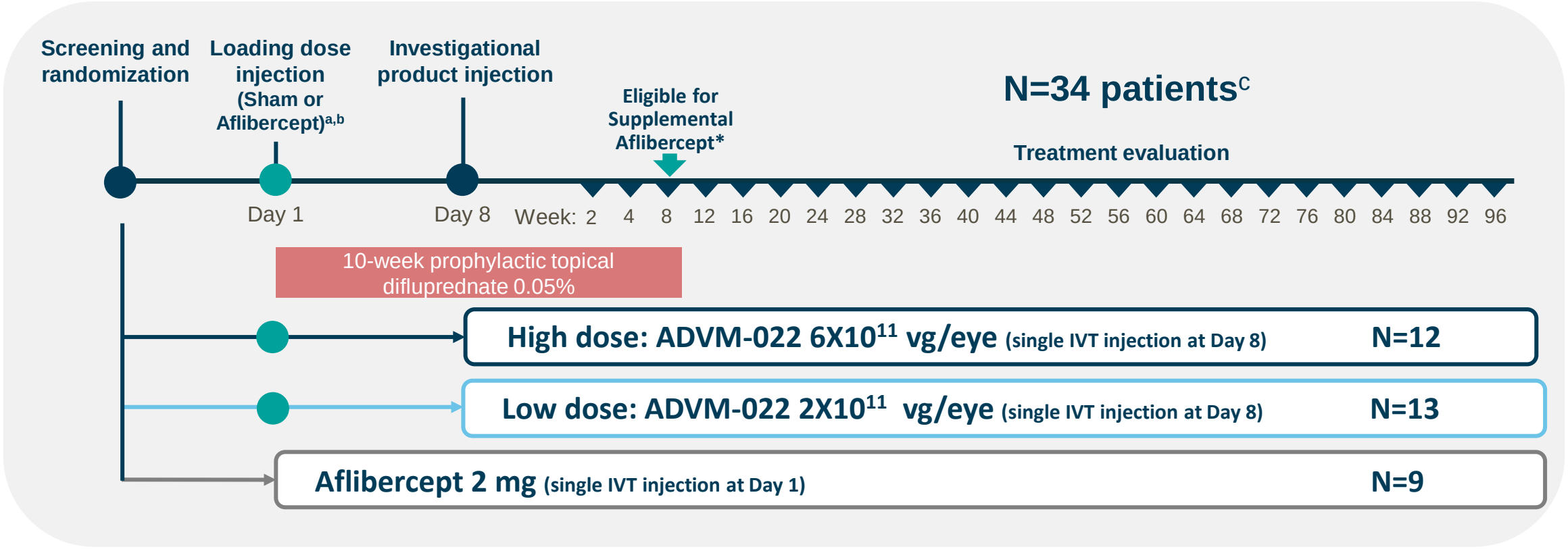
Safety Summary Across Cohorts

- 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 Phase 2 Study Design



- **Objective:** Assess the durability, safety and efficacy of a single IVT injection of ADVM-022 in patients with DME
- **Primary Endpoint:** Time to worsening of DME disease activity in the study eye (first supplemental aflibercept injection)

***Supplemental aflibercept criteria (2 mg IVT):**

Eligible starting week 8, with minimum 21 days between supplemental injections if meeting the conditions below:

- CST>50µm (relative to day 1 and week 4)
- Loss of >5 BCVA letters compared with the higher of two measurements recorded on day 1 or week 4

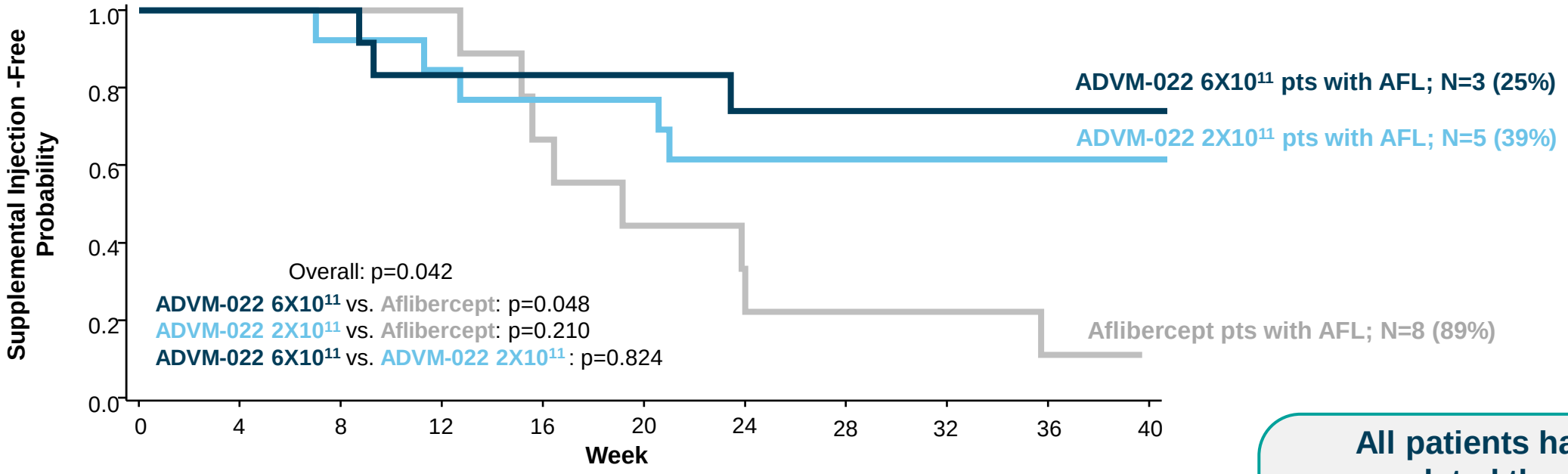
AFL, aflibercept; BCVA, best corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; IVT, intravitreal.
[a]Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.
[b]Aflibercept arm received aflibercept at Day 1. [c]36 patients randomized.
https://www.clinicaltrials.gov/ct2/show/NCT04418427

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

INFINITY Study: Week 24 Primary Endpoint – Time to worsening of DME disease activity

Kaplan Meier Curve: Proportion of Patients Supplemental Aflibercept Injection Free Over Time

Time to Disease Worsening (First Supplemental Injection)[a]



Number who Reached Visit (Number At-Risk)

ADVM-022 6X10¹¹	12 (12)	12 (12)	12 (12)	12 (10)	12 (10)	12 (10)	12 (7)	9 (5)	7 (5)	4 (4)	3 (3)
ADVM-022 2X10¹¹	13 (13)	13 (13)	13 (12)	13 (11)	13 (10)	13 (10)	11 (7)	7 (5)	6 (3)	4 (3)	3 (1)
Aflibercept	9 (9)	9 (9)	9 (9)	9 (9)	9 (6)	9 (4)	9 (3)	6 (2)	4 (2)	4 (1)	2 (0)

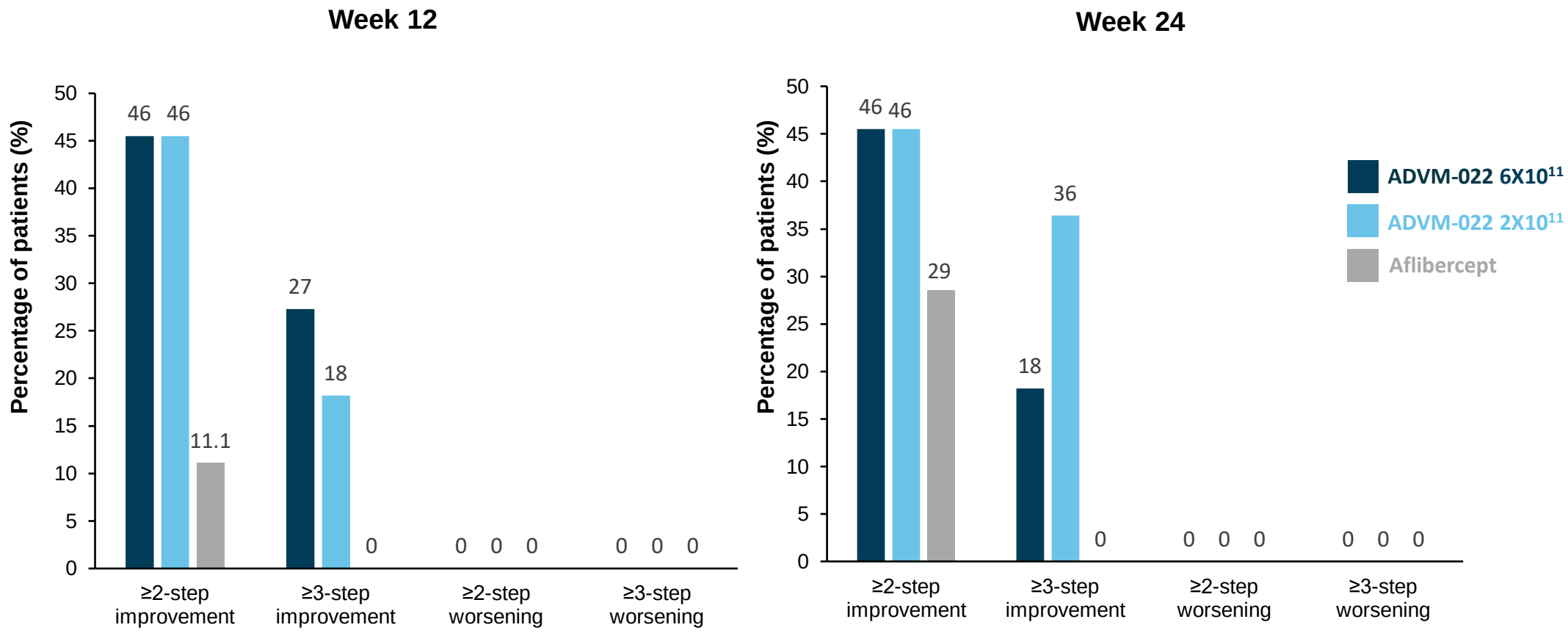
All patients have completed through ≥ Week 24

Median Follow-up approximately 30 weeks

AFL, aflibercept; BCVA, best corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; Pts, patients.
[a]Supplemental aflibercept criteria (2 mg IVT): (1) Not eligible for supplemental aflibercept until week 8 (minimum 21 days between injections); (2) CST>50µm (relative to day 1 and week 4); (3) Loss of >5 BCVA letters compared with the higher of two measurements recorded on day 1 or week 4.
Patients with inflammation in the ADVM groups resulted in excessive steroid use, which confounds the interpretation of efficacy results.
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

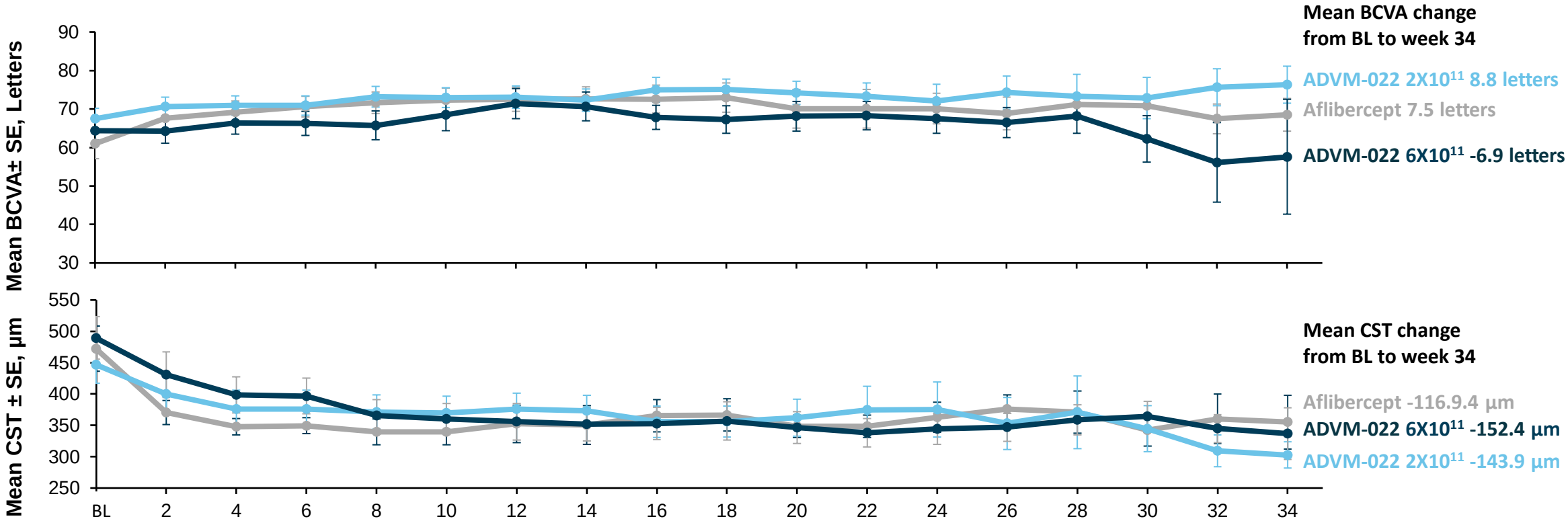
Improvement in DRSS in DME Patients Treated with ADVM-022



DME, diabetic macular edema; DRSS, diabetic retinopathy severity scale.
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

BCVA and CST in INFINITY over 34 Weeks[a]



Sample size:																		
ADVM-022 6X10^{11}	12	12	12	12	12	12	12	12	12	12	12	12	12	10	9	8	7	4
ADVM-022 2X10^{11}	13	13	13	13	13	13	13	13	13	13	13	12	11	10	7	7	6	6
Aflibercept	9	9	9	9	9	9	9	9	9	9	9	9	9	9	6	6	4	4

BCVA, best corrected visual acuity; BL, baseline; CST, central subfield thickness; DME, diabetic macular edema.
[a]Data were cut to week 34 because the sample size was <4.
Inflammation patients treated with ADVM resulted in excessive steroid use, which confounds the interpretation of efficacy results.
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

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INFINITY Study: More DME Patients in the ADVM-022 Cohorts Experienced IOI Compared to the Aflibercept Cohort

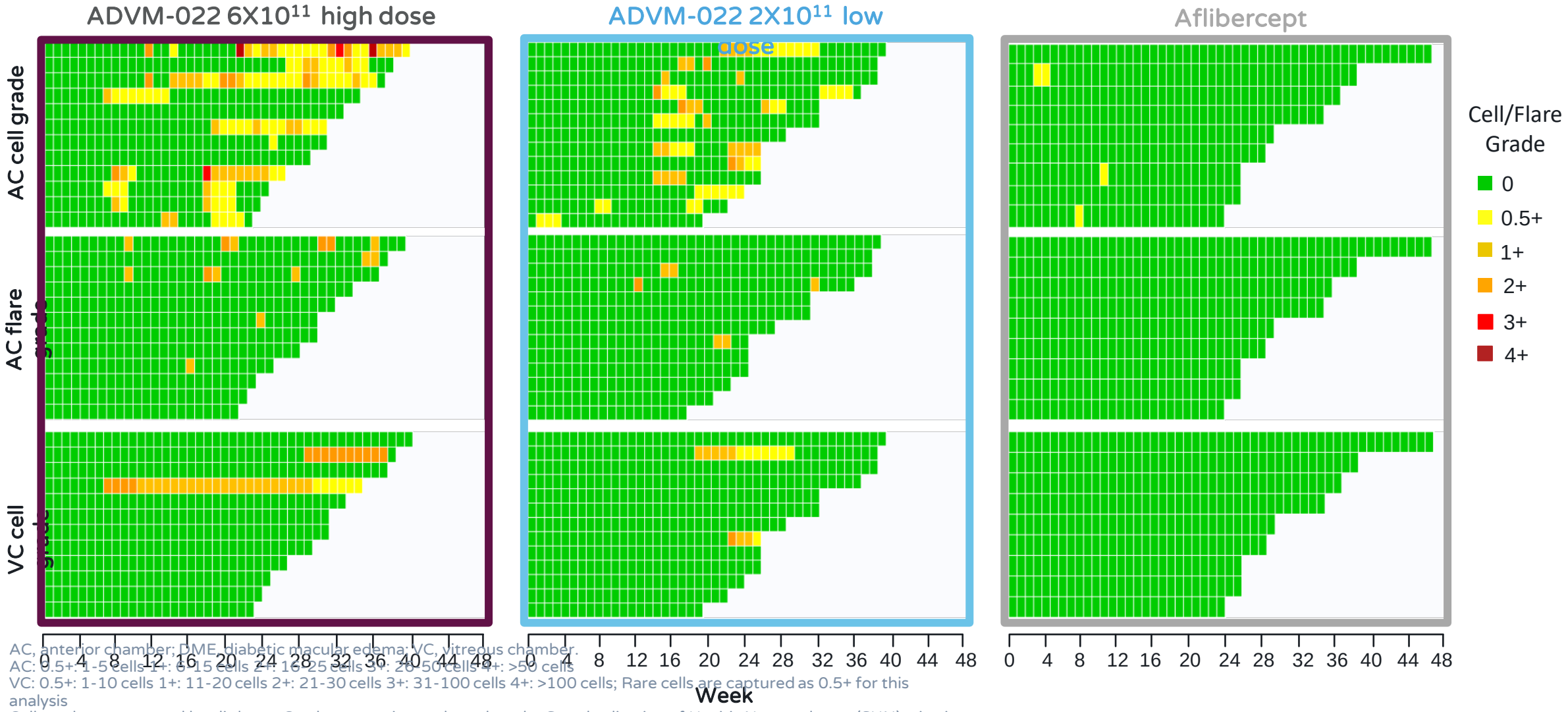
	ADVM-022 6X10^{11} (N=12)		ADVM-022 2X10^{11} (N=13)		Aflibercept (N=9)	
	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Ocular SAE[a]	**2 (17)**	**3**	**0 (0)**	**0**	**1 (11)**	**1**
Any IOI	**10 (83)**	**20**	**12 (92)**	**20**	**3 (33)**	**3**
Any Anterior IOI	9 (75)	18	11 (85)	19	3 (33)	3
Any Posterior IOI	2 (17)	2	1 (8)	1	0 (0)	0
Vasculitis / Endophthalmitis	0 (0)	0	0 (0)	0	0 (0)	0
Any Iris-Related Event	**8 (67)**	**16**	**7 (54)**	**17**	**0 (0)**	**0**
Transillumination Defects (any severity)	6 (50)	6	4 (31)	4	0 (0)	0
Synechiae	5 (42)	5	4 (31)	4	0 (0)	0
Pigmentary Changes (Anterior)	5 (42)	5	6 (46)	9	0 (0)	0
Hypotony	**3 (25)**	**3***	**0 (0)**	**0**	**0 (0)**	**0**

ADVM-022-related AEs were 57% mild, 41% moderate, and 2% severe

DME, diabetic macular edema; IOI, intraocular inflammation; SAE, severe adverse event.
[a]3 Ocular SAEs for 6E11: Hypotony, Worsening of Anterior Uveitis, Increase in Cells; 1 Ocular SAE for Aflibercept: Worsening Cataract. n (%) of participants with event reported in each dose group reported. Aflibercept/Sham was dosed on day 1. Subsequent aflibercept injections based on supplemental aflibercept criteria starting at Week 8. Five Total Cases of Hypotony. Three occurred prior to the data cutoff. Two occurred after the data cutoff. Three required surgery.

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

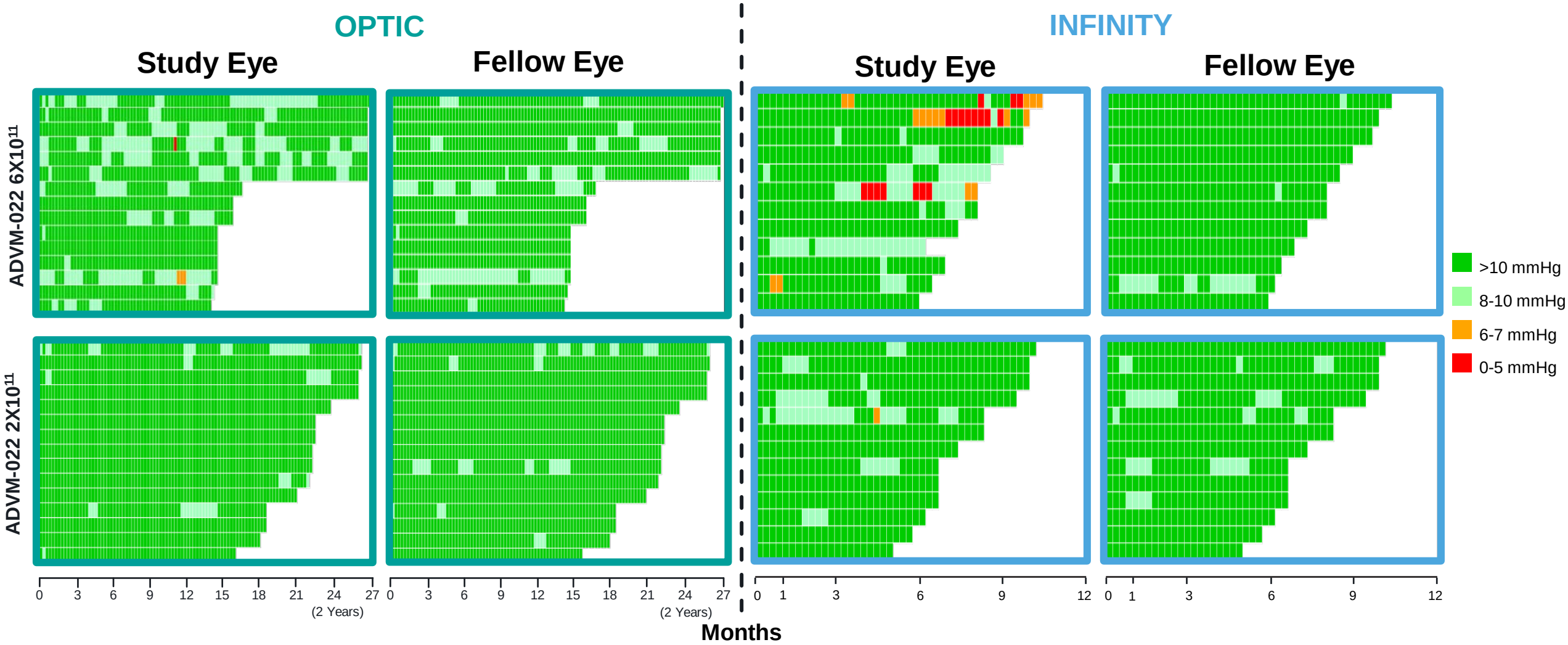
Dose-Dependent Inflammation Observed in DME Patients Over Time



AC, anterior chamber; DME, diabetic macular edema; VC, vitreous chamber.
AC: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 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
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.
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 and INFINITY Studies: IOP in Study Eye and Fellow Eye is Comparable at the 2x10^{11} vg/eye Dose



Three patients in the ADVM-022 6x10^{11} arm of the INFINITY study 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.

INFINITY Data cut off: June 22, 2021; All data unmasked: May 4, 2021; OPTIC Data cut off: July 16, 2021

OPTIC and INFINITY Studies: Safety Summary

- **ADVM-022 dose & disease state appear to have an impact in determining the therapeutic window which balances efficacy and safety**

OPTIC Study (nAMD)	INFINITY Study (DME)
• Minimal ocular inflammation 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%)‡ • No ADVM-022-related non-ocular adverse events*	• Dose-dependent inflammation was observed in DME patients with dose-limiting toxicity at $6x10^{11}$ vg/eye • 3 patients in $6x10^{11}$ vg/eye developed hypotony that required surgical intervention • All $6x10^{11}$ vg/eye patients required additional treatments for inflammation beyond difluprednate • No clinically relevant reduction in IOP was observed in the $2x10^{11}$ vg/eye group • The difference in safety profiles between the OPTIC and INFINITY studies highlight the need to consider the severe comorbid nature of patients with DME (including renal impairment and failure):

- **ADVM-022 development plan will focus on nAMD and low doses ($2x10^{11}$ vg/eye and lower)**

†*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).*
**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. Both were unrelated to study drug*
One unrelated ocular SAE of retinal detachment surgically repaired and resolved (Cohort 1)
IOP, intraocular pressure; AEs, adverse events; SAEs, serious AEs.

1. Kiel JW et al, *Prog Retin Eye Res.* 2011;30(1):1-17. 2. Flemmer J et al, *Eur Heart J.* 2013; 34: 1270–1278.
3.Hayashi M et al, *Br J Ophthalmol.* 1989;73:621-623. 4. Katamay and Nussenblatt. *Retina.* 2013: 579-589

ADVM-022 Acknowledgments

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